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**TOPIC HIGHLIGHT (Page 243-260):**
**Exercise Testing in Children with Congenital Heart Disease**

# JOURNAL OF CARDIOLOGY AND THERAPY

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TOPIC HIGHLIGHT

# Thematic Issue: Exercise Testing in Children with Congenital Heart Disease

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## EDITORIAL

Physical inactivity is considered as a cardiovascular risk factor in adults. Also in children, physical inactivity is often associated with disease. More specifically children with congenital heart disease (CHD) often were quiescent or did not perform the same activities as their healthy peers.

Exercise tolerance can be assessed by history taking or with questionnaires, but is has been shown that misclassifications were found by using these questionnaires with overestimation of up to 30% of the level of physical activity[1]. Therefore exercise tolerance has to be determined by exercise testing preferentially with respiratory gas exchange measurements. In this thematic issue, three review articles are published with a common theme of the assessment of exercise performance in children with congenital heart disease, both operated and non-operated.

The first chapter is dedicated to new concepts in the assessment of exercise tolerance in children with CHD. In this contribution, a new assessment paradigm that optimizes the use of exercise test results to promote physically active lifestyles is recommended. The assessment of physical literacy and an expanded use of the data available from a maximal cardiopulmonary exercise test are discussed in this light.

Since exercise capacity can change in growing children, a second chapter describes the value of serial exercise testing in children with CHD. Regularly repeated assessments of an individual's exercise function can therefore provide unique and valuable insights into the capabilities and cardiovascular health of patients with CHD. Serial exercise testing might as such provide important information both for the assessment of the current health status as for the estimation of the long term outcome of children with CHD.

And finally one contribution will demonstrate the usefulness of exercise testing in the clinical decision making regarding children with a left- to right shunt. Furthermore, in this review, the effects of abolishing left-to right shunt on exercise capacity, both early and late after closure will be summarized.

We hope that readers will enjoy this issue, obtain useful information, and be inspired with new ideas for the implementation and more expanded use of exercise testing in children with CHD.

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TOPIC HIGHLIGHT

# Exercise Tolerance in Children with a Left to Right Shunt

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## ABSTRACT

A left-to-right shunt lesion exists when blood from the left atrium, left ventricle, or aorta transits to the right atrium or its tributaries, the right ventricle, or the pulmonary artery. In these conditions blood from the systemic arterial circulation mixes with systemic venous blood. The presence of a left-to-right shunt results in a volume overload of one or more cardiovascular chambers or structures. Multiple factors influence the extent of flow through the shunt and its physiologic effects.

If the shunt is significant, blood flow and pressure in the pulmonary circulation become abnormally high. At the same type the amount of blood which reaches the systemic circulation (cardiac output) can be reduced, particularly during exercise. Over time, there is progressive damage to the pulmonary vasculature endothelium and gradual development of irreversible pulmonary vascular changes and pulmonary hypertension. The resistance in the pulmonary circulation may ultimately exceed the systemic resistance with reversal of blood flow from the right side of the circulation to the left (Eisenmenger syndrome) evident as cyanosis either at rest or during exercise.

Lesions resulting in left to right shunts include: (1) Atrial septal defect (ASD); (2) Ventricular septal defect (VSD); (3) Patent ductus arteriosus (PDA); (4) Large coronary artery fistulas.

While wide consensus exists in the management of significant shunts, it is not always clear when and how it is time to intervene on smaller defects. We will review the evidence supporting a role of exercise testing in the assessment of children and adults with left-to-right shunt and the effect of abolishing left-to right shunt on exercise capacity, both early and late after closure. No data is available in the literature on exercise capacity in patients with PDA or coronary artery fistulas. Therefore our work will focus on ASDs, which have been widely studied, and, to a lesser extent, VSDs.



**Key words:** Exercise tolerance; children; Left-to-right shunt; Atrial septal defect (ASD); Ventricular septal defect (VSD); Patent ductus arteriosus (PDA); Large coronary artery fistulas

Cervi E, Giardini A. Exercise Tolerance in Children with a Left to Right Shunt. *Journal of Cardiology and Therapy* 2015; 2(1): 244-249 Available from: URL: http://www.ghrnet.org/index.php/jct/article/view/1029

## ATRIAL SEPTAL DEFECTS PROPOSED

Atrial septal defects are the most common form of congenital heart defect and occur in 1 child in 1,500 live births[1]. Of the various types classified in base of the anatomic location, ostium secundum ASDs represent 6% to 10% of all cardiac anomalies.

In the setting of a large inter-atrial communication, a chronic left-to-right shunt creates a volume overload on the right-sided cardiac structures and results in dilation of the right atrium and right ventricle. The chronic volume overload causes dilation of the entire pulmonary vascular bed. Pulmonary blood flow is increased, often up to three to four times normal. However, the pulmonary artery pressure is only slightly increased, and in most patients, pulmonary resistance remains in the normal range.

Most infants and children with ASDs are asymptomatic. Rarely, ASDs are associated with poor growth, recurrent lower respiratory tract infection, and heart failure. Children with large left-to-right shunts are likely to complain of some fatigue and dyspnea.

The natural course of ASDs is relatively benign except for those with persistent significant left-right shunt. Typically, patients with smaller ASDs remain active and asymptomatic through early childhood, and many patients have lived into their fourth, fifth, sixth, and even seventh decades with ASDs of moderate size before

symptoms developed[2].

Congestive heart failure rarely is found in the first decades of life, but it becomes more common with advancing age. The same can be said for the incidence of atrial arrhythmias with the associated risk of stroke and paradoxical embolism[1]. In a few patients (5-10%) with a secundum ASD, severe and irreversible hypertensive pulmonary vascular disease may develop[3].

As cardiac catheterisation used to performed as a diagnostic step in many patients with an ASD, indication on closure was predominantly based on haemodynamic data, particularly the extent of the ratio between pulmonary blood flow and systemic blood flow (Qp/Qs). It is generally accepted that elective closure of ASD is the treatment of choice if pulmonary-to-systemic blood flow ratio is >1.5. However, many children now do no undergo cardiac catheterisation as a diagnostic step and invasive criteria have been replaced by echocardiographic criteria. The main criteria for posing the indication to ASD closure is the presence of more than mild right heart dilatation or signs of increased right ventricular systolic pressure in the face of significant left-right shunt (which can also measured by echocardiography). Additional qualitative criteria are the presence of increased venous return from the pulmonary veins and dilatation of the main pulmonary artery.

Elective surgical repair of ASDs has been a safe and simple operation in the hands of an experienced surgical team. It has been the first treatment of choice for children with large defects in the last 50 years and there is a large body of medical research covering long term results. Since most ASDs are well tolerated in infancy and may spontaneously close, elective repair frequently has been deferred until the child is at least 4 years of age.

Trans-catheter techniques for closure of ostium secundum ASDs have been available for several years. In 1976, King *et al* reported the first trans-catheter closure of a secundum ASD in humans with a double-umbrella device[4]. The availability of non surgical ASD closure has led to an increase in the number of the defects being closed[5] and has perhaps also lowered the bar for some defects to be considered for closure. Trans-catheter closure has the advantage of avoiding the need for sternotomy, cardiopulmonary bypass and intensive care stay and facilitates rapid patient recovery when the anatomy of the defect is suitable. However still nowadays younger patients or those with very large defects or small/absent defect margins require surgical closure.

## EXERCISE TOLERANCE IN CHILDREN TREATED FOR ASD

Data are now available on long term follow-up of patients who underwent surgical ASD closure during childhood. Despite a clear improvement in the morbidity of these patients, there is still ongoing debate on whether children with ASD which undergo surgical closure can achieve the same life expectancy of healthy peers if treated timely. Cuypers *et al* recently published very long-term (30-41 years) outcome after surgical ASD closure in childhood and showed excellent survival and low morbidity. The general health and exercise capacity of the patients reported were comparable to the healthy Dutch population. They reported no pulmonary hypertension but persistent right ventricular dilation at magnetic resonance imaging despite a long follow-up from closure[6]. In the recent study by de Koning *et al*, exercise testing did not reveal differences between patients who underwent surgical ASD closure in childhood and healthy reference population. In line with Cuypers *et al* they found right ventricular end-systolic volume remained increased in the long term after surgical closure without any impact on exercise capacity or onset of arrhythmias[7].

Only one study, by Massin *et al*, compared the outcome of children who underwent percutaneous ASD closure versus open surgery. The study showed no difference in peak $VO_2$ but underlined a higher prevalence of chronotropic incompetence in the surgical group, even though this didn't affect overall exercise capacity[8]. In this setting chronotropic incompetence is thought to be secondary to the effect of the cannulation used to establish cardiopulmonary bypass. Previous studies showed a significant reduction in exercise tolerance in children with ASD[9] and failed to show a significant improvement after trans-catheter closure[9,10]. Reasons for that might be the fact that study cohorts were small and that the follow up was limited to 3 months, when research in young adults suggests that the process of normalisation of exercise capacity can take significantly longer than 3 months[11]. No data is currently available on long term outcome of percutaneous closure in children.

## EXERCISE TOLERANCE IN ADULT PATIENTS TREATED FOR ASD

At present ASDs accounts for up to 40% of congenital heart lesions detected in adults 40 years of age and older[12]. Despite high pulmonary blood flow and right heart volume overload, patients with uncomplicated ASD often report only minor subjective complaints and do not recognise their reduced exercise tolerance. This is evident from the fact that several studies have shown reduced exercise capacity even in asymptomatic patients[13,14]. Nakanishi and colleagues tested 18 adult ASD patients and found their peak$VO_2$ was impaired (21.6±5.6 mL/min/kg or 63.5±16.2% of predicted). They also observed that higher PAPm and higher Qp/Qs were related to lower exercise capacity[12]. Oelberg *et al* tested 10 adults with ASD and compared them to 10 matched healthy controls. Their patients were found to have reduced exercise performance, which could be associated with an abnormal increase in pulmonary artery pressure during exercise[15].

In the past when only surgical procedures were available, only large ASDs would be advised for closure because they were considered likely to result over time in shunt reversal or heart failure. Adults with significant ASDs are advised to undergo surgical repair before the onset of pulmonary hypertension in order to increase longevity and limit the deterioration of functional capacity. Once pulmonary hypertension develops, irreversible right ventricular failure may result. However, it can be difficult to detect early stages of pulmonary vascular damage when pulmonary arterial pressures and pulmonary vascular resistance are still normal at rest but they can rise, instead of physiologically decrease, during exertion[16].

Surgical series have shown discordant results on functional status following surgical ASD closure in adult patients, giving rise to concerns on the appropriate timing of intervention and patients selection. Fredriksen *et al*. compared exercise capacity in adults with congenital heart disease with healthy subjects and found that even patients with closed ASDs did not do as well as controls in the long term[17]. However, Helber *et al* showed a lack of improvement in exercise capacity early after surgical ASD closure in patients over the age of 40 years, but they suggested that the improvement in exercise capacity took place later as demonstrated by the complete normalisation observed 10 years after shunt closure[18]. They observed that the improvement in exercise tolerance didn't correlate with the size of the shunt but it correlated inversely with mean pulmonary pressure before closure. Kobayashi *et al* reported a larger cohort and

**Table 1** studies testing cardiopulmonary capacity in children with ASDs.

| Study | Pts | Pre closure peak $VO_2$ (mL/kg/min) | Pre closure peak $VO_2$ (% of predicted) | Group | Age at closure (years) | Qp/Qs | PAPm (mmHg) | RVSP (mmHg) | Age at CPET (years) | Fup CPET | Ppost closure peak $VO_2$ (mL/kg/min) | post closure peak $VO_2$ (% of predicted) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cuypers [5] | 63* | - | - | S | 7.5±3.5 | **2.3** | - | - | **43±4.8** | 35±2.7 y | - | 96 | $VO_2$ within the normal range |
| de Koning 2013[6] | 38^ | - | - | S | 4.6±2.8 | - | - | - | 16.7±2.9 | - | 38.8±7.7 | - | $VO_2$ within the normal range |
| | 32 | 41±13 | - | C | - | - | - | - | 16.3±3.7 | - | - | - | |
| Massin 2009[7] | 18 | - | - | S | 7.8±2.8 | 2.8±0.5 | - | - | - | 2.9±2.7 y | - | - | No difference between surgical and percutaneous closure, $VO_2$ was within the normal range |
| | 20 | - | - | P | 8.3±2.8 | 2.6±0.4 | - | - | - | 2.6±2.4 y | - | - | |
| Rhodes 2002[8] | 9 | - | 91±15 | P | 13 (7-48) | 1.9±0.7 | 16.8±3 | - | - | 2 (1-7) m | - | 90±18 | No significant difference pre-post ASD closure<br>$VO_2$ was within the normal range |
| Pfammatter 2002[9] | 16 | 40.8 (27.8-44.9) | - | S/P | 11.4 (6.8-16.1) | - | - | - | | 3 m | 37.8 (28.5-48.6) | - | ASD pts had a significantly reduced $VO_2$ which didn't improve after closure irrespectively of shunt relevance |
| | 15 | 44.3 (30.9-52.3) | - | C | - | - | - | - | - | - | - | - | |

Legend. pts: patients; $VO_2$: oxygen consumption; group: kind of treatment; Qp/Qs: pulmonary flow/systemic flow; PAPm: mean pulmonary arterial pressure; RVSP: right ventricle systolic pressure; CPET: cardiopulmonary exercise test. * 63 pts underwent CPET of the 135 pts cohort described; ^ 38 pts underwent CPET of the 42 pts cohort described.

**Table 2** Studies testing cardiopulmonary capacity in adults with ASDs.

| Study | Pts | Pre closure peak $VO_2$ (mL/kg/min) | Pre closure peak $VO_2$ (% of predicted) | Group | Age at closure (years) | Qp/Qs | PAPm (mmHg) | RVSP (mmHg) | Age at CPET (years) | Fup CPET | Ppost closure peak $VO_2$ (mL/kg/min) | post closure peak $VO_2$ (% of predicted) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fredriksen 2001 [13] | 93 | - | | S | 25 (1-72) | - | - | - | 41 (17-71) | - | 19.8±7.3 | - | Adult pts with closed ASDs have a significant $VO_2$ reduction compared to controls |
| Helber 1997[14] | 31 | 13.1 | | S | 39.9±11.5 | 2.8±1.2 | 18.2±6.2 | - | - | 10 y | 27.0 | - | Significant $VO_2$ improvement at 10y (not significant at 4m fup), Improvement was not correlated to Qp:Qs but inversely correlated to PAPm |
| Kobayashi 1997[15] | 28 | 27.6±6.3 | | S: Qp:Qs<3 PAPm<30 | 42.3±15.9 | 2.5±0.4 | 26.8±6.1 | - | - | 3.7±1.4 m | 31.1±5.1 | - | No $VO_2$ improvement observed in the group with high PAPm<br>Significant $VO_2$ improvement in the other groups |
| | 28 | 19.3±5.7 | | S: Qp:Qs>3 any PAPm | 47.3±9.7 | 3.9±0.8 | 35.9±11.7 | - | - | 4.4±2.0 m | 21.5±2.1 | - | |
| | 14 | 17.6±3.6 | | S: Qp:Qs<3 PAPm>30 | 46.3±12.3 | 1.7±0.4 | 74.8±14.6 | - | - | 5.6±2.3 m | 17.8±2.8 | - | |
| Suchon 2009[16] | 52 | 23.4±8.9 | 64.3±18.0 | S | 38.6±15.0 | 2.6±0.7 | - | 36.7±11.3 | - | 1 y | 29.7±10.2 | 83.1±20.3 | Significant improvement in $VO_2$ at 1 y, no difference in the surgical/percutaneous closure; $VO_2$ didn't normalize in patients with RVSP>30 mmHg |
| | 48 | 23.5±3.1 | 70.4±12.0 | P | 42.4±13.0 | 2.4±0.7 | - | 33.3±10.7 | - | 1 y | 31.7±8.3 | 86.6±13.5 | |
| Van De Bruaene [17] | 18 | 26.7±10.6 | 79±19 | No closure | 39±19 | 1.6±0.9 | 24.1±6.7 | - | 41±17 | - | - | - | $VO_2$ within normal range after closure |
| | 10/18 | - | - | S/P | 34±20 | 1.9±0.8 | 25.9±8.3 | - | - | - | 24.8±8.5 | 88±18 | |
| Brochu [18] | 37 | 23.5±6.4 | - | P | 49.4 (19-76) | 2.1 (1.2-3.4) | - | - | - | 6 m | 26.9±6.9 | - | Significant $VO_2$ improvement |
| Takaya [19] | 20 | 15.4±6.5 | 53.6±6.5 | P | 54.5±10.9 | 2.6±0.6 | - | - | - | 1 y | 17.5±3.5 | 61.8±9.7 | Significant $VO_2$ improvement in pts>40 yo |
| Jategaonkar 2010[20] | 53* | 25.5±6.7 | - | P: 16-40 yo | 28.7±7.3 | 49±11.9% | 15.8±4.6 | - | - | 3 m | 27.7±7.0 | - | Significant $VO_2$ improvement at 3 months in all age groups if Qp:Qs>2 |
| | 54* | 20.9±5.6 | - | P: 41-60yo | 50.7±5.5 | 51.2±11.8 | 21.1±5.4 | - | - | 3 m | 23.0±6.2 | - | |
| | 47* | 16.8±5.3 | - | P: 61- 85 yo | 70.3±5.4 | 49.4±12.9 | 25.3±7.5 | - | - | 3 m | 18.8±5.1 | - | |
| J. 2009 [21] | 35^ | 17.1±5.5 | - | P | 69.9±5.3 | 48.7±12.6% | - | - | - | 33.6±31.2 m | 18.8±5.4 | - | In 60-84 yo pts $VO_2$ improvement is more significant if Qp:Qs>2 |
| Lange [22] | 24** | 23.6±2.1 | - | P | 50 (17-78) | - | - | - | | 24 m | 23.2±2.3 | - | $VO_2$ within normal range, no significant $VO_2$ improvement |
| Giardini [23] | 32 | 21.9±10.3 | - | P | 42.6±16.7 | 2.04±0.5 | 15.8±4.2 | - | - | 6 m | 25.6±9.9 | - | Significant $VO_2$ improvement in pts<40yo and QpQs>2 |
| Giardini [24] | 29 | - | 61.8±17.1 | P | 42.3±16.4 | 2.0±0.5 | 16±4 | - | - | 3.7±0.4 y | - | 88.8±12.4 | Further remodeling and $VO_2$ improvement in the long term |
| Trojnarska 2009[25] | 26 | 24.6±4.8 | | No closure | 43.2±8.9 | - | - | - | - | - | - | - | Significant $VO_2$ impairement compared to healthy controls |
| | 39 | 33.6±9.3 | 88.9±14.8 | Healthy controls | 35.8±9.3 | - | - | - | - | - | - | - | |
| Oelberg 1998[12] | 10 | 17.3±4.2 | - | No closure | 52.9±11.2 | 2.4±1.5 | - | 31±8 | - | - | - | - | Significant $VO_2$ impairement compared to healthy controls |
| | 10 | 22.9±5.4 | - | Healthy controls | 52.3±10.9 | 1.0±0.2 | - | 17±8 | | - | - | - | |

Legend. pts: patients; $VO_2$: oxigen consumption; group: kind of treatment; Qp/Qs: pulmonary flow/systemic flow; PAPm: mean pulmonary arterial pressure; RVSP: right ventricle systolic pressure; fup: follow up; CPET: cardiopulmonary exercise test. * 154 pts underwent CPET of the 332 pts cohort described; ^ 35 pts underwent CPET of the 96 pts cohort described; ** 24 pts underwent CPET of the 59 pts cohort described.

stratified patients on the basis of the size of the shunt and the degree of pulmonary arterial hypertension. No peak $VO_2$ improvement was shown in the group of patients with PAPm>30 mmHg, while those patients with significant shunts and lower pulmonary artery pressure did improve their exercise capacity following closure[19].

The importance of finding abnormal and possibly exercise-limiting elevations in pulmonary artery pressure during exercise in ASD might also be important in the decision making regarding the timing of surgical closure. Van de Bruaene *et al* demonstrated older patients who underwent closure later on in life had a good overall cardiopulmonary capacity but didn't normalise pulmonary haemodinamics, which was shown by the lack of physiological decrease of pulmonary vascular resistance on exertion[16].

In recent years trans-catheter closure has became widely available and the results have proven to be at lest as good as surgical closure in terms of mortality and functional capacity. Suchon *et al* compared the two techniques in an effort to demonstrate that, when dealing with favourable anatomy, percutaneous closure is a less costly option and guarantees the same results in the mid term. They demonstrated a low exercise capacity at baseline and a significant increase in oxygen uptake after both surgical and trans-catheter closure, as well as a significant decrease in minute ventilation/$CO_2$ dioxide output. Their patients improved significantly their exercise capacity, irrespective of the actual method of closure, but patients with elevated right ventricular systolic pressures failed to normalise their peak $VO_2$[20].

Brochu *et al* assessed the effect of percutaneous ASD closure in 37 asymptomatic or mildly symptomatic adults showing a significant and rapid improvement of exercise capacity and regression of right ventricular dilatation at 6 months. The improvement in exercise capacity was irrespective of age, functional class, right ventricular enlargement, or baseline exercise capacity[14].

Jategaonkar *et al* reported a significant decrease in right ventricular end-diastolic diameter and significant improvements of NYHA functional class and peak $VO_2$ at 3 months from ASD device closure in all age groups, even in patients over 60 years old. However, little is known about long-term results in those patients[21].

Our group evaluated the impact of trans-catheter ASD closure on right ventricular remodelling and exercise capacity in asymptomatic adult patients with the aim of identifying the factors associated with a change in exercise capacity. We demonstrated that the improvement in peak $VO_2$ is due to an improvement in peak $O_2$ pulse. We also demonstrated that an increase in both left ventricular stroke volume and cardiac output due to a positive ventricular interaction is the mechanism leading to increased peak $O_2$ pulse and peak $VO_2$[13]. We also demonstrated that the improvement is not limited to the 6 months period as a further cardiac remodelling and improvement in exercise capacity can be expected in the mid term[11,13]. Another observation from our group is that device ASD closure can quicken the time taken to recover from maximal exercise, which might also have positive implications for patients.

## VENTRICULAR SEPTAL DEFECTS

Ventricular septal defects account for approximately a third of the congenital cardiac defects diagnosed at birth. The magnitude of the left-to-right shunt is related directly to the size of the defect and pulmonary vascular resistance. Small VSDs are those less than one third the size of the aortic root and which impose a high resistance to flow with a resultant large pressure drop between the left and the right ventricle. In this case, the left-to-right shunt is small, right ventricular systolic pressure is normal, and there is no tendency for an increase in pulmonary vascular resistance.

With large VSDs, a gradual decline of pulmonary vascular resistance usually occurs in the first few months of life, resulting in augmentation of the left-to-right shunt. The large blood volume handled by the left atrium results in left atrial and pulmonary venous hypertension. The increased return to the left side of the heart results in an enlarged left atrium and left ventricle as well as an increase in the left ventricular muscle mass. With the marked volume overload of the left ventricle, congestive heart failure is particularly likely to occur between the ages of 2 and 8 weeks. Compensatory mechanisms that allow the infant to adapt to this volume load include the Frank Starling effect, increased sympathetic cardiac stimulation, and myocardial hypertrophy. The rapidity of the development of myocardial hypertrophy is one of the major factors in the ability of an infant to compensate adequately for a VSD with a large left-to-right shunt.

Excessive and high pressure pulmonary blood flow is associated with progressive pulmonary arterial vessel injury. Chronic injury associated with a large un-repaired VSD can result in a thickened adventitia, medial hypertrophy, and intimal injury resulting in pulmonary vascular obstructive disease[1]. Therefore, large VSDs with left-to-right shunt should undergo surgical repair within 1 year of age to prevent pulmonary vascular changes. Smaller defects can be followed up in time and a considerable portion is found to decrease in size and eventually spontaneously close[22,23]. The long term outcome of this latter group seems benign.

When children with surgically closed VSDs or those with haemodynamically insignificant defects have undergone ECG exercise testing results have generally showed normal exercise capacity[23-26]. A small number of studies concentrated on cardiopulmonary exercise testing in patients with VSDs. Binkhorst et al. showed no difference in peak $VO_2$ in patients after surgical VSD closure, small VSDs left untreated and healthy controls. Perrault at al. compared a small cohort of repaired VSD patients to patients with repaired tetralogy of Fallot, patients with repaired ASD and healthy controls and found peak $VO_2$ values were within the normal range in patients with closed VSDs. In both the previously mentioned studies, peak heart rate was found to be lower in surgical treated VSD patients, which is consistent with previous evidence of chronotropic limitations after cardiopulmonary bypass surgery in different types of congenital cardiac defects[27,28].

Moller *et al* described 44 patients (17 surgically closed ASD, 11 surgically closed VSD, 16 restrictive VSD considered haemodinamically not significant and thus left open) who underwent cardiopulmonary exercise testing and exercise echocardiography. They found reduced exercise capacity in all patients groups when compared to a control group comprising 88 healthy subjects. The authors observed an abnormal right ventricular systolic pressure response to exercise even in those patients who did not have any signs of increased pulmonary artery pressure at rest before closure. This finding was confined to VSD patients alone, either closed (5/11 patients) or open (4/16 patients), whereas no ASD patients showed increased pulmonary pressure during exercise[29].

## DISCUSSION

Patients with significant left-to-right shunt, particularly ASD patients, even if asymptomatic, have a significant exercise capacity limitation when compared to healthy controls[9,15]. Patients who are symptomatic, those with larger shunts and those with increased pulmonary artery pressure can be particularly limited.

Patients with ASD, like many other children with congenital heart defects, generally adapt to their limitation which is present since early infancy and describe themselves as asymptomatic, even when their exercise capacity is clearly reduced[13,29,30]. Therefore, indication for closure can not rely on symptoms which are generally late, when complications have already developing. There are no available longitudinal data on exercise capacity in untreated ASD patients but early cross-sectional evaluations suggested symptoms usually develop during adulthood and the natural history of the disease is not benign in the long term[3].

While we agree on ASD closure when a large shunt is detected during childhood, debate is still ongoing in older patients with smaller shunts or large shunts that eventually caused borderline pulmonary vascular damage with slight and/or reversible raise in pulmonary arterial pressures. Age does not seem a determinant of the response to ASD closure as over 40 years old seem to improve their peak $VO_2$ in a similar fashion to those patients below 40 years of age[13,14]. Even though there is an association between change in peak $VO_2$ and size of the left-to-right shunt, patients with smaller shunts (like those with a Qp/Qs <2) also show some clinically significant improvements in their exercise capacity after closure[13,14].

After surgical closure right ventricular dimensions change dramatically and exercise capacity greatly improves. However, whereas in children exercise capacity gradually reaches normal values in the long term[7], peak $VO_2$ fails to reach predicted values in adult patients with preoperative signs of pulmonary hypertension[20].

Due to its less invasive nature with short recovery time and low morbidity and mortality, percutaneous closure has becoming the first choice treatment in older children and adults with a suitable anatomy. The first small studies on trans-catheter closure showed no significant difference in peak $VO_2$ after closure[9,10]. Larger subsequent studies showed that percutaneous ASD closure led to an improvement in exercise capacity regardless of age at ASD closure[21] and symptoms, but proportional to the amount of left-to-right shunt and pulmonary artery pressure[11,19]. Data from our lab[13] have shown that the left-to-right shunting of blood does not only cause pulmonary over-circulation (both at rest and during exercise) but also causes a reduction in systemic perfusion, both at rest and during exercise. We also showed that the improvement in peak $VO_2$ after ASD closure is a consequence of increased left ventricular stroke volume and cardiac output. ASD closure augments left ventricular filling, thereby increasing left ventricular preload, left ventricular end-diastolic diameter and ultimately left ventricular stroke volume. At the same time the right ventricle decreases in size, paradoxical septal motion disappears and ventricular interaction improves.

Peak $VO_2$ improvement was observed with both surgical and percutaneous closure series[8,20]. Improvements were as early as 3 months post-op, particularly after percutaneous closure because of the reduced recovery time, but they appear to continue over time with further increase in exercise capacity in the mid-term[7,11]. However, postoperative exercise capacity was reported lower than in normal subjects[31] presumably because of low cardiac output during exercise due to reduced heart rate response during exercise[32], or a low level of daily physical activity after surgical closure of ASD which is observed also in children with other types of congenital heart disease. Furthermore an inappropriate response of the pulmonary vasculature to exercise may also have a large influence on postoperative exercise capacity.

Studies looking at cardiopulmonary responses to exercise in VSD patients have shown mixed results with some studies showing some limitation in peak $VO_2$ related to increased right ventricular systolic pressure during exercise whereas other studies have shown no evidence of significantly reduced exercise tolerance either when considering large VSDs after closure or small VSDs in natural history. However, all studies were of small size and therefore no generalisation can be made for the overall VSD population. Children with Down's syndrome and congenital heart defects have a higher predisposition to develop pulmonary hypertension[33] and this is due to many different factors that can be controlled or modified only to a minor extent[34]. Therefore, exposure to long-standing increased left-to-right shunt flow where sheer stress on endothelium induces endothelial dysfunction followed by irreversible remodelling of pulmonary arteries, may have a worse effect in subjects with Down syndrome compared to non-syndromic children[35]. These children and young adults are therefore more likely to have their exercise capacity affected by changes in the pulmonary vasculature and should receive early treatment[29].

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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TOPIC HIGHLIGHT

# Serial Exercise Testing in Patients with Congenital Heart Disease

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## ABSTRACT

Cardiovascular function is an important determinant of exercise function. Formal exercise testing can therefore provide clinically useful, quantitative and objective insights into a patient's cardiovascular status. Serial exercise studies evaluate the progress of an individual patient's exercise function over a period of time and provide clinicians with a unique perspective upon the natural history of congenital heart disease. They can also provide quantitative, objective data regarding the functional impact of various clinical interventions and often shed light on important physiologic processes that otherwise might not be appreciated.



**Key words:** Heart disease; Congenital; Exercise test; Oxygen consumption

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## WHY LONGITUDINAL AND SERIAL STUDIES?

Cross-sectional studies of exercise function, because they provide only a snapshot of a group of patients at a single point in time, leave clinicians with many unanswered questions. For instance, cross-sectional studies cannot determine whether a patient with poor exercise function has experienced a progressive decline over time, or has always had a similar degree of exercise dysfunction[1]. In the world of pediatric cardiology this issue is also complicated by the fact that the field has evolved rapidly over the past few decades. Innovations, both great and small, have dramatically affected the life expectancy and quality of life of patients with congenital heart disease. Researchers are therefore confronted by a clinical landscape that is always changing, in constant motion. Understanding the natural, or unnatural, history of individual congenital heart defects in this setting is therefore a complex affair and the inherent limitations of cross-sectional studies emerge as serious shortcomings. For example, if a study were to find that older subjects with a particular congenital heart defect performed less well than younger subjects, the study would be unable to unambiguously determine whether this observation was related to an era effect, i.e., less sophisticated cardiologic care available to the older subjects when they were young, or to a natural, time-related decline associated with the heart defect itself and unrelated to the medical advances achieved during the patients' lifetime. Indeed, the snapshots that cross-sectional studies provide are often blurred and hard to interpret.

Longitudinal studies (which, for the purpose of this paper, will be defined as studies that observe the natural evolution of exercise function in the absence of an intervention, in contrast to the term "serial exercise studies", which will refer to exercise tests performed before and after an intervention), on the other hand, evaluate the progress of individual patients over a period of time. They therefore can convey a more accurate and reliable picture of the natural history of congenital heart defects in the current era. The influence of era effects are also more readily appreciated and assessed.

The clinical importance of longitudinal exercise testing arises from the fact that the primary function of the cardiovascular system is to supply blood flow (and oxygen) in quantities sufficient to support the metabolic needs of the body. This function is maximally stressed

during physical activity (i.e., exercise)[2]. Longitudinal assessments of an individual's exercise function can therefore provide unique and valuable insights into the capabilities and cardiovascular health of patients with congenital heart disease. These considerations also apply serial exercise studies, which can provided clinicians with objective, quantitative data regarding the effect of a cardiovascular intervention upon a patient's exercise function.

## TECHNICAL ISSUES RELATED TO LONGITUDINAL STUDIES AND SERIAL EXERCISE TESTS

Body size and exercise capacity change rapidly during the pediatric years. These changes are especially dramatic during puberty. Furthermore, although gender-related differences in exercise capacity exist prior to puberty, these differences become more pronounced during and after the pubertal years. Exercise capacity also continues to change during adulthood. On average, peak $V_{O2}$ declines by ~0.7%/year after age 21[3]. Consequently, when comparing exercise test data from studies performed on an individual at different ages, the potential implications of these natural changes must be borne in mind. Because prediction equations (ideally) take these considerations into account, for peak $V_{O2}$ and related variables [e.g., the oxygen pulse and the $V_{O2}$ at the ventilatory anaerobic threshold (VAT)], it is usually best to express data as a percentage of predicted values, especially when the studies include patients in the pediatric and adolescent age groups[2]. It must be noted, however, that the most commonly employed pediatric prediction equations were derived more than three decades ago in a group of 109 normal subjects[4]. More recent studies have raised concerns about the applicability of these equations in the current era[5]. Some have also suggested that account should be taken of seasonal changes in exercise function[6].

Other exercise-test variables may also vary with age. For instance, Giardini *et al* recently reported that the $V_E/V_{CO2}$ slope declines during the pediatric years and then rises again during adulthood. When interpreting data from longitudinal studies, account must be taken of these natural changes as well[7].

Patient effort can have a dramatic effect upon peak-exercise variables. Consequently, when comparing peak-exercise data from serial exercise tests, it is essential to ensure that an adequate effort was expended on both tests. Otherwise, the potential confounding effects of variable patient effort will make comparison of serial peak-exercise data uninterpretable or misleading. To achieve this goal, physiologic criteria for an adequate effort should be applied. Acceptable criteria include a respiratory exchange ratio (RER) $\geqslant$1.09 at peak exercise and/or a peak heart rate >85% of predicted at peak exercise (in the absence of a tachyarrhythmia)[2]. Some investigators claim that the anaerobic metabolic pathways are less developed in children and therefore suggest that, for young subjects, a lower RER may be a more appropriate threshold[8]. Of course, issues related to patient effort do not apply to data derived from submaximal exercise, e.g., the $V_{O2}$ at the VAT and the $V_E/V_{CO2}$ slope.

## CLINICAL UTILITY OF SERIAL EXERCISE TESTS

Serial exercise tests can provide quantitative, objective data regarding the benefits and/or effectiveness of therapeutic interventions that are undertaken for patients with congenital heart disease. The results of these studies are sometimes surprising and can reveal important physiologic phenomena that might otherwise be overlooked. A few studies selected from the pediatric cardiology literature, which illustrate these points, will now be briefly reviewed.

Helber *et al* studied the exercise function of 31 adult patients before and after surgical ASD repair. Prior to surgery, the patients' exercise capacity was severely depressed (peak $V_{O2}$ 13.1 mL/kg/min; ~50% of predicted). Four months post-operatively peak $V_{O2}$ increased minimally (13.6 mL/kg/min). However, when tested 10 years post-op, peak $V_{O2}$ had increased to normal levels (27.0 mL/kg/min; ~95% predicted). Similar patterns were observed for the peak work rate and the $V_{O2}$ at the ventilator anaerobic threshold. The lack of improvement in exercise function at the 4 month post-operative visit was thought to be due to the debilitation associated with the trauma of surgery and inactivity during the convalescent period. The subsequent improvement in exercise function was attributed to a training effect that accompanied the resumption of normal physical activities. These observations underscored the important interaction between the cardiovascular and skeletal muscle systems[9].

In 2008, Meadows *et al* reported the results of serial exercise tests in 20 Fontan patients before and after fenestration closure. Although transcatheter Fontan fenestration closure had previously been shown to engender an acute increase in arterial oxygen saturation, the procedure was also known to be associated with an acute decrease in systemic cardiac output and oxygen delivery. The sum result of these physiologic changes upon exercise capacity of Fontan patients had never been examined. The authors found that, although baseline and peak-exercise arterial oxygen saturations improved significantly after fenestration closure, there was no change in peak $V_{O2}$ (70.9±18.6% to 74.0±18.6%, $p$=NS), heart rate, or $O_2$ pulse at peak exercise. They explained these findings by noting that, at peak exercise, oxygen uptake by the lungs is dependent upon the mixed venous oxygen saturation and the pulmonary blood flow, which in turn is determined the mean pulmonary artery pressure, the pulmonary vascular resistance and the mean left atrial pressure. Because oxygen extraction is maximized at peak exercise (and mixed venous oxygen saturation falls to the same low level, whether or not a fenestration is present), and because fenestration closure is unlikely to have a large impact upon the Fontan patient's pulmonary vascular resistance, pulmonary artery or left atrial pressure at peak exercise, fenestration closure is unlikely to have a dramatic effect upon peak $V_{O2}$. The authors also observed, however, that the $V_E/V_{CO2}$ slope fell in 20/20 patients after fenestration closure, and the end tidal $pCO_2$ at the VAT rose in 19/20 patients. This observation was attributed to the reduction in right to left shunting $CO_2$-rich blood following fenestration closure[10].

In contrast to the observations in Fontan patients, Rhodes *et al* reported that the peak $VO_2$ of a patient with a large physiologic right to left shunt secondary to a pulmonary AV fistula improved following transcatheter occlusion of the fistula. In that case, the patent fistula impeded blood flow to the alveoli during exercise. Occlusion of the fistula allowed more blood to flow to the alveoli at peak exercise and thereby permitted greater oxygen uptake by the lungs at peak exercise. As with the Fontan patients, the elimination of the $CO_2$-rich right to left shunt blood also engendered a decline in the $V_E/V_{CO2}$ slope and an increase in end tidal $pCO_2$[11].

The results of serial exercise tests in tetralogy of Fallot patients undergoing pulmonary valve replacement surgery have been mixed. Some have found an improvement in exercise function[12], others have not[13-15]. The discrepancies are probably due, in part, to the time interval between the surgery and the post-operative exercise test; improvements in exercise function may not be observed until the deconditioning associated with the surgery and convalescence is reversed.

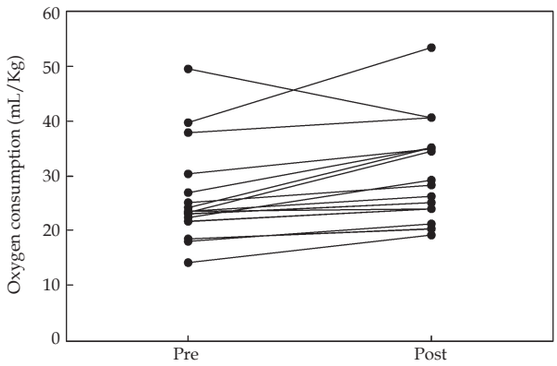


**Figure 1** Effect of cardiac rehabilitation program on patients with congenital heart disease. Peak oxygen consumption rose in 15/16 subjects following cardiac rehabilitation; overall, oxygen consumption increased an average of 22% above baseline, pre-rehabilitation values. Pre: Pre-rehabilitation; Post: post-rehabilitation (From: Rhodes J *et al* Impact of cardiac rehabilitation on the exercise function of children with serious congenital heart disease. Pediatrics. 2005; 116:1339-1345 From: Rhodes J *et al* Impact of cardiac rehabilitation on the exercise function of children with serious congenital heart disease. *Pediatrics*. 2005; **116**: 1339-1345.)

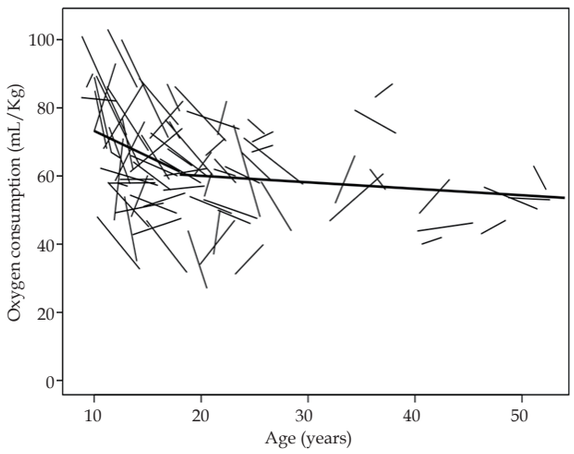


**Figure 2** Longitudinal exercise function of patients following the Fontan procedure. Each thin line represents the regression line of exercise tests from an individual patient. The thick lines represent the average of all patients' regression lines before and after age 18 years. Percent predicted peak VO2 fell steeply prior to age 18; the decline was much more gradual thereafter. From: Fernandes SM *et al* Serial cardiopulmonary exercise testing in patients with previous fontan surgery. *Pediatr Cardiol*. 2010; **31**: 175-180.

Several serial studies have documented acute improvements in the exercise function of patients with congenital heart disease have following participation in a formal exercise rehabilitation program (Figure 1)[16-19]. Sustained benefits (more than 6 months after the termination of the rehabilitation program) have also been observed in rehabilitation subjects, but not in a group of control subjects with similar congenital heart defects observed during the same period[20].

## RESULTS OF LONGITUDINAL STUDIES OF EXERCISE FUNCTION IN CONGENITAL HEART DISEASE

There exists in the literature only a small number studies that have focused upon the longitudinal exercise function of patients with congenital heart disease. In a study of 98 Fontan patients with serial exercise data, Fernandes et al found that the %predicted peak $V_{O2}$ of patients with Fontan physiology tends to decline steeply during late childhood/adolescence and more slowly thereafter[21]. The decline in peak $V_{O2}$ appeared to be due primarily to a decline in the oxygen pulse at peak exercise. It was also associated with an increase in the $V_E/V_{CO2}$ slope during exercise. Multivariate analysis revealed that progressive impairment of the chronotropic response to exercise also accounted for some of the decline in peak $V_{O2}$.

The observed steep decline in peak $V_{O2}$ during late childhood/adolescence was attributed to the large increase in skeletal muscle mass that is associated with puberty. In normal individuals, this increase in muscle mass is accompanied by a commensurate increase in the ability to augment cardiac output (and oxygen delivery) during exercise. Consequently, peak $V_{O2}$ (in mL/min) normally increases dramatically during the course of the adolescent years. However, unlike patients with normal, biventricular circulations, the Fontan patient's ability to increase cardiac output during exercise is limited. The increase in peak $V_{O2}$ that is normally associated with puberty is therefore attenuated; consequently, % predicted values decline. The authors also observed that the decline in peak $V_{O2}$ is more pronounced among male subjects compared to female subjects, and attributed this observation to the fact that the increase in muscle mass associated with male puberty typically exceeds that associated with female puberty[21]. Giardini *et al* also analyzed serial exercise data from 53 patients with Fontan physiology. They too found a progressive decline in peak $V_{O2}$[22]. In contrast, Nir *et al* reported that the exercise function of 25 patients who had undergone a Fontan procedure between 1977 and 1989 remained stable[23]. The initial peak $V_{O2}$ of these patients from the early Fontan era was much lower than that reported in the more recent studies; this discrepancy probably accounted for the slower decline in Nir *et al*'s series.

Kipps *et al* analyzed serial exercise data from 70 patients who had undergone repair of Tetralogy of Fallot. They found a small annual decline in %predicted peak $V_{O2}$. The decline was very variable, however. Once again, it was strongly associated with a concomitant decline in the oxygen pulse at peak exercise. An association between the decline in peak $V_{O2}$ and a concomitant increase in the $V_E/V_{CO2}$ slope was also observed. Statistically significant associations were not observed between the rate of decline of %predicted peak $V_{O2}$ and numerous clinical, echocardiographic and CMR variables[24].

In another study, Kipps *et al* also analyzed longitudinal exercise data of 23 patients with Ebstein's anomaly. They observed a decline in %predicted peak $V_{O2}$. The decline was steeper among patients <18 years of age. A decline in the oxygen pulse accounted for most of the decline in peak $V_{O2}$. Multivariate modeling revealed that a decrease in the heart rate at peak exercise also contributed to the decline in peak $V_{O2}$[25].

In 2004, Roos-Hesslink *et al* reported the results of serial exercise tests in 50 patients with d-TGA palliated by a Mustard procedure.26 They found that the maximal exercise capacity of these patients averaged 84% of predicted in 1990 and declined to 72% of predicted in 2001. %Predicted peak heart rate did not decline during this time period. In contrast, Matthys *et al* detected no change in the exercise capacity during 6-17 years of follow-up in 16 patients who had undergone atrial switch procedures for d-TGA[27].

Reybrouck *et al* reported the results of longitudinal exercise studies in 79 patients with a variety of congenital heart defects[28]. These authors found that the $V_{O2}$ at the VAT of patients with simple defects, who were not restricted from physical activity, remained

stable during the follow-up period. In contrast, patients with medically-imposed physical restrictions and/or significant residual hemodynamic lesions decreased significantly over time. In 2013, Muller *et al* reported the results of longitudinal exercise studies in 522 patients with a variety of congenital heart diseases. They observed a slow (1.01±6.83 percentage point/yr) decline in peak VO2 that appeared to be independent of diagnosis, heart disease severity, systemic ventricular morphology or age. The decline appeared to be steeper among patients who had a pacemaker[1].

In summary, longitudinal studies have provided interesting and potentially important insights into the natural history of exercise function in patients with repaired congenital heart defects. They have revealed that a gradual deterioration in exercise function is common. In many patients and for many defects, deconditioning probably accounts for some of the decline. Undoubtedly other lesion-specific, reversible and irreversible phenomena also contribute to this process; the exact role of each factor remains to be elucidated.

Other studies have found that congenital heart disease patients with poor exercise function have a much higher mortality risk than those with well-preserved exercise function[29-32]. The progressive decline in exercise function that has been observed in many longitudinal studies is therefore quite concerning. Are there any interventions that can effectively interrupt or reverse the decline in exercise function? Is a steep, sudden decline more concerning than a gradual decline? Serial exercise studies have demonstrated that various interventions can achieve acute, and sometimes sustained, improvements in exercise function. Will these improvements become associated with an improved long-term quality of life and a decreased mortality risk? Additional studies are needed to address these questions.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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TOPIC HIGHLIGHT

# New Concepts in the Assessment of Exercise Capacity Among Children with Congenital Heart Disease: Looking beyond Heart Function and Mortality

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## ABSTRACT

Cardiopulmonary exercise testing is a valuable tool in the diagnosis and management of pediatric congenital heart disease. Parent and child reports of the child's physical activity relative to peers are also routinely used to monitor heart function. Unfortunately, objective measures of their physical activity indicate that most children with congenital heart disease lead sedentary lives, which increase their risk of secondary morbidities. Current recommendations emphasize the need to proactively counsel patients to engage in at least 60 minutes of physical activity daily. Information regarding the child's current capacity for physical activity can be obtained through a physical literacy assessment and enhanced use of cardiopulmonary exercise results. Physical literacy is the knowledge, motivation, behaviour and physical competence needed to adopt and maintain a physically active lifestyle. Protocols to assess these physical literacy domains are well established, with the Canadian Assessment of Physical Literacy offering the first comprehensive assessment of all domains. Cardiopulmonary exercise protocols that incorporate sub-maximal stages, and measures of the child's willingness to perform maximal intensity exercise provide important information about the child's capacity for physically active play with peers, which seldom requires a maximal effort. Measures of physical literacy and sub-maximal cardiorespiratory capacity thus provide important information when counselling children with congenital heart defects and their parents regarding the child's daily physical activity participation.



**Key words:** Physical activity; Sedentary lifestyle; health risks; counselling; physical literacy; health-related fitness

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## INTRODUCTION

Exercise testing has been a staple in the care of children with congenital heart defects for more than 25 years[1]. The gold standard exercise test throughout this time has been maximal exercise capacity, typically measured with a bicycle or treadmill protocol. Results from the maximal exercise test are reported as the percentage of predicted maximal oxygen consumption ($VO_2$) achieved. The maximal exercise test provides important information about heart function, arrhythmias, and cardiac output during exercise[2]. Maximal exercise capacity is known to be associated with mortality and morbidity among children with corrected congenital heart defects[3].

Currently more than 95% of children with non-critical and 70% of children with critical congenital heart defects survive to adulthood[4]. As such, clinical and research attentions have turned toward secondary morbidity and quality of life. Children with congenital heart defects are known to lead sedentary lifestyles[5] that persist into adulthood[6]. These sedentary lifestyles increase the risk for secondary morbidities such as hypertension, obesity, diabetes, and acquired heart disease[7]. Given the long-term implications of sedentary lifestyles for children with congenital heart defects, the American

Heart Association has published a scientific statement (May 2013) on the promotion of physical activity to individuals with congenital heart defects[8]. The AHA statement suggests that clinicians should proactively promote physical activity to all individuals with congenital heart defects during every clinical encounter, and that physical activity, fitness and motor skill should also be assessed.

Research among healthy individuals has demonstrated that moderate amounts of daily physical activity have a substantial impact on health and quality of life[9]. In order to optimize the health benefits of physical activity, international recommendations state that children should perform at least 60 minutes of physical activity daily[10-14]. Research with children with congenital heart defects has demonstrated that daily physical activity may be reduced even when maximal exercise capacity is age-appropriate[6,15-19]. As a result, an assessment that only measures maximal exercise capacity may not provide the information needed to appropriately counsel patients about physical activity or assess the risk of morbidities associated with a sedentary lifestyle.

## A NEW ASSESSMENT PARADIGM

In order to optimize the long-term health and quality of life of children with congenital heart defects, a new assessment paradigm that optimizes the use of exercise test results to promote physically active lifestyles is recommended. The new paradigm would incorporate a variety of exercise assessments within two broad categories: (1) physical literacy; and (2) expanded use of the data available from a maximal cardiopulmonary exercise test. Assessment results from these sources can provide important information about children's physical activity, and the barriers that limit their participation.

## ASSESSMENT OF PHYSICAL LITERACY

Physical literacy is the attributes, skills, characteristics and behaviours that enable a physically active lifestyle[20]. Unlike traditional concepts of fitness or exercise capacity, physical literacy considers the impact of a much broader range of factors that may impact physical activity, such as motor skill, knowledge and understanding, motivation or daily behaviour. Taken together, physical literacy represents the child's capacity to achieve and maintain a physically active lifestyle. The Canadian Assessment of Physical Literacy is a valid and reliable measure of the physical literacy of children 8 to 12 years of age. It provides an overall measure of physical literacy, as well as sub-domain scores for motivation and confidence, knowledge and understanding, physical competence and daily behaviour[21]. The benefits and limitations of the Canadian Assessment of Physical Literacy are briefly summarized in figure 1. Detailed protocols are available at www.capl-ecsft.ca. Simple screening tasks, suitable for administration in healthcare settings, that can identify children who are struggling on their physical literacy journey are currently being evaluated (unpublished data). Comprehensive, valid and reliable protocols to assess a broad spectrum of physical literacy components among young children or adolescents have not yet been published, although individual protocols for specific aspects of physical literacy (e.g., accelerometry for daily behaviour, handgrip dynamometry for muscular strength) are available.

### Assessment of Motivation and Knowledge

The concept of assessing a child's motivation for physical activity often seems counterintuitive because most adults believe that children are naturally active. Parents will say that their children never sit still or that keeping up with their children is exhausting, and yet objective measures of their activity indicate that they spend their discretionary time in primarily sedentary pursuits[22]. We know that motivation, confidence and self-efficacy for physical activity are critically important to the physical activity participation of healthy children[23,24]. Youth with congenital heart disease indicate that physical activity is not a valued pursuit and experiences of exclusion, low self efficacy, fatigue and covert fears combine to further decrease physical activity motivation[25]. Research suggests that the severity of the cardiac defect does not have a direct effect on physical activity participation. Rather individual beliefs about self-efficacy for physical activity, the recommendations provided by the cardiologist and parental attitudes are of primary importance[26].

A comprehensive assessment of the many facets of knowledge (activity opportunities, rules, skill development, recommended behaviours, etc.) and motivation (enjoyment, social support, adequacy, benefits, etc.) that influence childrens' physical activity participation would be difficult to administer. There are many published questionnaires that assess motivation for physical activity, but most are designed for adults (e.g., RM 4-FM (Deci & Richard); Processes of Change (Marcus & Forsyth; Exercise Motivations Inventory (Markland); Physical Activity Enjoyment Scale (Kendzierski & DeCarlo)). Questionnaires specifically for children (Children's Self-perceived Adequacy and Predilection for Physical Activity[27] often include assessment components specific to school physical education, rather than or in addition to the more general concept of physical activity. The questionnaire component of the Canadian Assessment of Physical Literacy (www.capl-ecsfp.ca) is designed to assess the physical activity knowledge and motivation of children 8 to 12 years of age. The questionnaire can be completed online, and automated scoring provides feedback regarding the child's physical literacy knowledge and motivation. Most healthy children have knowledge and motivation levels that are lower than what is considered adequate for physical literacy. Preliminary data among children who have congenital heart defects indicate that they obtain similar results (unpublished data).

It is important that clinicians counselling children with congenital heart defects regarding physical activity consider the knowledge and motivation of the child, as well as the knowledge and motivation of significant adults who care for the child. Support for the child's physical activity among immediate family members is very important, but the knowledge and motivation of other adults (e.g., teachers, day care providers, parents of other children) should also be considered. Developing sufficient motivation for physical activity and the acquisition of knowledge regarding appropriate physical activity opportunities are the foundation of the earliest stages of behaviour change[28]. Patients will begin to contemplate changing their physical activity behaviour only when they become aware of the need for change. In order to move from contemplation to the preparing for action stage, patients must develop sufficient motivation for physical activity and resolve any ambivalence towards a change in behaviour[28,29]. Clinicians should explore the child's physical activity interests as well as the physical activity resources available when counselling patients and families. It is also helpful to introduce the child/family to a broad range of appropriate physical activity opportunities to ensure that a lack of knowledge or uncertainty about activity does not inappropriately restrict the child's participation. Research indicates that over 40% (33/81) of parents of children with congenital heart defects have questions or concerns about their child's physical activity participation (unpublished data).

Table 1 Examples of Health-Related Fitness Protocols (reprinted from Longmuir et al, 2013[8]).

| Health-Related Fitness Dimension | Examples of Assessment Protocols |
|---|---|
| Cardiorespiratory fitness | 20-metre shuttle run, 15-metre shuttle run, modified Canadian Aerobic Fitness Test. |
| Flexibility | Sit and reach, Back-saver sit and reach. |
| Muscular strength | Handgrip strength, Standing broad jump, Vertical jump, Bosco jump protocol. |
| Muscular endurance | Plank static hold, Partial curl-up, Curl-up, Bent-arm hang, Push-up. |
| Body composition | Waist circumference, Body mass index, Waist-to-hip ratio, Sum of skinfolds. |

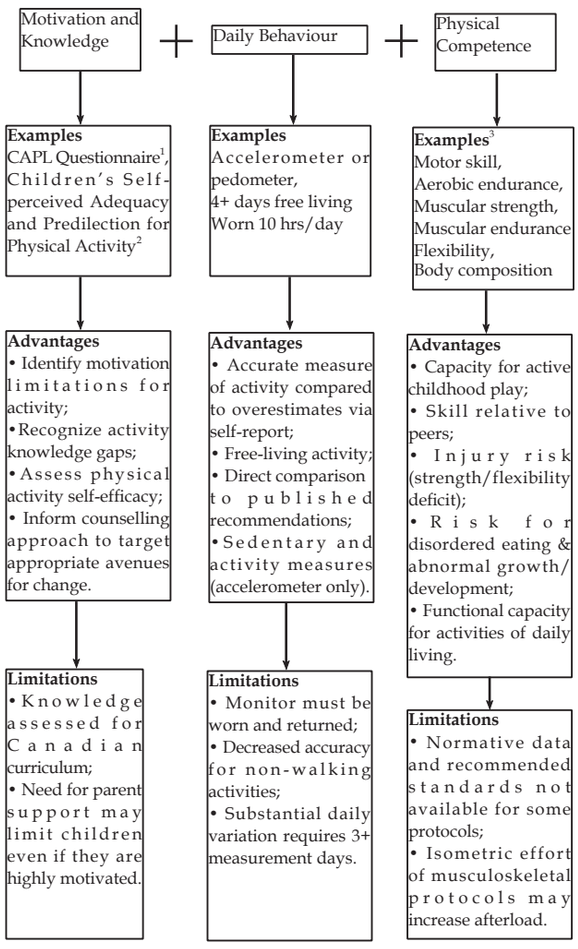


**Figure 1** Physical Literacy Assessment Paradigm.
[1] CAPL questionnaire: motivation and knowledge components of the Canadian Assessment of Physical Literacy are available online (www.capl-ecsfp.ca);
[2] Hay JA. Adequacy in and predilection for physical activity in children. Clin J Sport Med 1992;2:192-201.
[3] CAPL assessment protocols are: obstacle course (motor skill), PACER shuttle run (aerobic endurance), hand grip dynamometry (muscular strength), plank isometric hold (muscular endurance), sit and reach flexometer (flexibility), body mass index (body composition).

**Assessment of Daily Behaviour**

Asking patients about their physical activity participation is a well-established practice in paediatric cardiology. Physicians inquire about the types of activity the child performs, whether the child can do as much physical activity as peers, and whether any symptoms occur with exertion. In relation to supporting children with congenital heart defects to achieve the physically active lifestyle associated with optimal health, this traditional approach has several limitations. First, it relies on child self- or parent proxy-reports of the child's physical activity. Research has clearly demonstrated that subjective reports of physical activity participation are very inaccurate. There is low to fair agreement between parent and child reports of the child's physical activity[30] and the reported physical activity levels differ significantly from objective measures[31]. Children considered inactive based on accelerometer measures of daily activity were reported to be active by 80% of parents and 40% of the inactive children themselves[31]. Among patients with congenital heart disease, the inaccuracy of subjective estimates of exercise capacity has also been demonstrated[32,33] even among those who reported being asymptomatic[32]. An additional limitation is the use of peers as a reference for the child's activity level. Studies provide conflicting evidence as to whether children typically achieve the recommended level of physical activity[22,34]. For North American children[22,35] at least, most healthy peers lead sedentary lifestyles such that "being able to keep up with peers" does not represent a physically active lifestyle.

Pedometers and accelerometers are devices that measure walking steps or body acceleration, respectively. Pedometers provide a measure of the child's physical activity, while accelerometers can measure both sedentary and active behaviours. Population-based data for typical values among children as well as recommended levels for optimal health are available for both types of measures. Children should accumulate at least 12,000 steps per day[36] or at least 60 minutes per day of activity that is of moderate or higher intensity[10-14]. Accelerometers are considered more accurate, particularly for non-walking activities, but they are also more expensive ($200-$400 versus $10-$15 or less). More recently, pedometers that also estimate time spent in moderate-to-vigorous activity have been developed[37]. All of these devices are very small, making them suitable for even young children[38,39]. Most are water-resistant and are worn on the waist or wrist. Due to the high day-to-day and within-day variability of children's physical activity, 7 days of pedometer or accelerometer measurements with the device worn for at least 10 hours per day are recommended[40], although physical activity can be estimated from a minimum of 4 days (including 1 weekend day).

Objective measures of daily behaviour are valuable when counselling patients regarding physical activity because the data can dispel misconceptions about the child's level of activity. Measures of sedentary time are typically very high, on average 7 to 8 leisure hours per day for adolescents[22]. Data on the high amount of discretionary time spent in sedentary pursuits can counteract the most commonly cited barrier to increasing physical activity – a lack of time. Even when very few children achieve the daily physical activity recommendation, most children will achieve the recommended activity level on at least 1 day per week[36]. These data can be helpful in counselling children and parents that achieving the recommended activity level is possible for children with a congenital heart defect. They also demonstrate the feasibility of the recommended behaviour change. Although children with congenital heart defects are often

sedentary[6,41], evidence that a physically active lifestyle is feasible for these patients can be seen in children with the most complex congenital heart defects who are able to achieve the recommended 60 minutes of daily activity[19] even in the presence of significant limitations to maximal exercise.

**Assessment of Physical Competence**

The physical competence domain within physical literacy refers to the motor skill, body composition and health-related physical fitness required to successfully participate in physical activity. Standardized protocols for assessing children's health-related fitness (aerobic endurance, muscular endurance, muscular strength, flexibility) and body composition are well established (examples in table 1 and Bar-Or and Rowland, 2004[42]). Traditional assessments of motor skill are more limited because many established protocols are designed to identify children with motor skill deficits or to focus primarily on younger children[43-46], which may limit their usefulness in describing the motor skill of typically developing children[47]. The Canadian Assessment of Physical Literacy combines an obstacle course assessment of motor skill with health-related fitness assessments (PACER shuttle run[48] for aerobic endurance, plank isometric hold for muscular endurance[49], handgrip for muscular strength[50], sit and reach for flexibility[50], and height, weight and waist circumference for body composition[50]) to indicate the child's physical competence for a physically active lifestyle.

Physical competence assessment results contribute valuable information when counselling children with congenital heart defects regarding a physically active lifestyle. The intermittent activity that characterizes the play of younger children[51] depends much more heavily on skill, strength, flexibility, and balance than aerobic endurance. Older youth also identify a perceived lack of skill as being a primary barrier to participation[25]. As such, the physical activity participation of children with congenital heart defects is typically not disadvantaged because of cardiac function or maximal exercise limitations, and even those with cardiac limitations can successfully participate[52]. In fact, some studies have suggested that children with complex heart defects may perform sub-maximal aerobic exercise as or more efficiently (i.e., with similar or lower levels of energy expenditure) compared to healthy peers[53,54]. Unfortunately, sedentary lifestyles, which are adopted by many children with congenital heart defects, are associated with decreased health-related fitness[55] and motor skill[56]. Thus, the decreased physical competence often observed among children with congenital heart defects is hypothesized to result primarily from their "hypoactive" lifestyles[6]. Fortunately, exercise training[57,58] and increased physical activity[59] can improve the fitness and motor skill of children with simple and complex congenital heart defects.

## ENHANCED USE OF CARDIOPULMONARY EXERCISE TEST RESULTS

As summarized by Rhodes and colleagues[2], maximal cardiopulmonary exercise tests provide important information regarding the cardiopulmonary function of patients with congenital heart defects. Most directly, these maximal effort tests indicate the child's capacity for high intensity physical activity. However, the physiological changes that occur in response to an exercise stimulus can also provide important information regarding cardiovascular status, such as the response to changing vascular pressures, heart rate limitations due to sinus node dysfunction, or the impact of ventricular dysfunction, residual shunts or valvular disorders[2]. When interpreting test results, it is important to determine whether the highest values attained represent a truly maximal effort (and therefore represent the individual's maximum cardiorespiratory capacity) or simply the peak voluntary effort that was generated during the assessment. Maximal exercise capacity is primarily (40% to 70%) influenced by genetics[60]. Established criteria for a maximal effort in children include a plateau in oxygen consumption despite increased workload (which only occurs in about 50% of children), a heart rate of at least 195 beats/minute, a blood lactate concentration of 9 mmol/litre or a respiratory gas exchange ratio that exceeds 1.0[42].

While information on the function of the cardiovascular system during maximal exercise is beneficial for disease management, the health benefits of daily physical activity accrue with moderate intensity activity[11,13]. Thus, cardiopulmonary exercise protocols that incorporate sub-maximal exercises stages of at least 3 minutes duration (e.g., Bruce treadmill protocol) can provide important information to enhance physical activity counselling even in the absence of a maximal effort. Normative data for the heart rate response of children at each stage of the Bruce protocol[61] provide important information regarding the child's capacity for daily physical activity and active play with peers. Sub-maximal exercise response is also an effective way to monitor the effects of training over time, as the energy and effort required for a given workload will decrease as physical fitness improves even in the absence of changes to maximal exercise capacity. The target activity intensity to increase cardiorespiratory fitness in children is an intensity of 60% to 80% of maximal exercise capacity[42]. Children as young as 7 years of age can be taught to monitor and maintain their target exercise intensity based on perceived exertion[62]. When counselling children with congenital heart defects and their families, it is important to educate families on the differences between maximal and typical exercise, as well as how the child's capacity is suited for the typical energy demands of childhood physical activity[42,63].

## CONCLUSION

Physically active lifestyles are important for the physical and mental health of children with congenital heart defects. Exercise assessments should include measures of physical literacy, as well as sub-maximal cardiorespiratory capacity. These results provide a more accurate and comprehensive picture of the child's capacity for a physically active lifestyle, and are the foundation for providing effective physical activity counselling to the child and family.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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CASE REPORT

# Tako-Tsubo Cardiomyopathy through Adalimumab

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## ABSTRACT

A 66-year old woman was admitted with typical clinical signs of angina pectoris. In her history only a chronic rheumatoid arthritis, treated through Adalimumab was reported. The electrocardiograph (ECG) showed sinus rhythm with terminal negative T-waves in V1-V6 without any ST-elevations. Laboratory tests revealed a positive Troponin-I level and the transthoracic echo showed a reduced left ventricular (LV) function by apical akinesia. We immediately performed cardiac catheterization to rule out the suspected coronary artery disease and documented surprisingly a Tako-Tsubo Cardiomyopathy with severe reduced LV function and signs of apical ballooning. Personnel distress, feeling of severe pain, any kind of anger, or anxiety could not be stated in the case history. A further invasive electrophysiological testing ruled out arrhythmias as trigger mechanisms for the Tako-Tsubo Cardiomyopathy. We stopped the Adalimumab therapy and could directly illustrate improved LV function to the normal status under resolved healthy conditions. This is the first time to report Adalimumab as cause for Tako-Tsubo Cardiomyopathy while there is to date literally no direct effect of TNF-alpha antibodies on the myocardium published - lacking any sympathetic nervous stress.



**Key words:** Tako-Tsubo Cardiomyopathy; Adalimumab; sympathetic nervous stress

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## LEARNING OBJECTIVES

The new TNF-alpha antibody Adalimumab - given to treat rheumatoid Arthritis may causes Tako-Tsubo Cardiomyopathy.

## INTRODUCTION

Tako-Tsubo Cardiomyopathy is a cardiac distress syndrome triggered through sympathetic nervous stress like anger, anxiety, pain, dyspnoea[1] or others[2]. Due to the reversible manner of the disease, (1) all findings resolve without further specific treatment[2] and (2) there are only betablockers established to reduce the recurring occurrence of the disease[3]. In the literature, other mechanisms are described triggering Tako-Tsub Cardiomyopathy. i.e. patients applied with Trastuzumab or with immunglobulines[4]. Here, first and exclusively, we are demonstrating a new tumor necrosis factor-alpha antibody (TNF-alpha antibody: Adalimumab) as potential trigger for Tako-Tsubo Cardiomyopathy lacking any sympathetic nervous stress.

## CASE REPORT

A 66-year old woman was admitted to the hospital with typical pressure pain on the left chest as well as tenderness on palpitation since 3 days. Historically, she is suffering a chronic rheumatoid arthritis set on Adalimumab [40mg subcutaneously per 2 weeks, tumor necrosis factor-alpha (TNF- alpha)-antibody] given second time, 3 days prior to admission as well as on Methotrexat (10 mg per week) linked by Hydrocortisone (5 mg daily) in remission phase. Distress situations were declined: there is no history of personnel

stress, anger, pain, dyspnoea, or anxiety. Further, no tachycardia could be reminded.

Clinically we found a woman in a good general condition and normal nutritional status, awake, oriented, her blood pressure 120/70mmHg, her pulse 62/min., her respiratory rate was normal, 14/min., oxygen saturation of 97%, no pathologic murmurs, auscultation of the lungs reveals no bilateral wheezes and rales, unobtrusive physical examination. Auscultation of the heart revealed normal findings.

Laboratory tests resulted positive for troponin I (0.78ng/m), other laboratory values (particularly inflammation parameters) were within normal range. The electrocardiographic (ECG) showed a sinus rhythm at the rate of 62/min., terminal negative T waves in V1-V6 as well as remarkable (non Pardee-Q) Q-waves in III, aVF (Figure 1). X-ray of chest revealed complete normal. The transthoracic echocardiography showed reduced left ventricular function, ejection fraction was determined to 40% using Simpson's equation with akinetic apical walls of all regions (Figure 2). In respect to the supposed non-ST-elevation myocardium infarction (NSTEMI), we immediately performed an invasive cardiac catheterization to rule out the suspected coronary artery disease. All coronary arteries were inconspicuous, clean and smoothly perfused (Figure 3). Further, we illustrated severe reduced left ventricular function with signs of typical ballooning in respect to Tako-Tsubo Cardiomyopathy (Figure 4). Clinically, the tenderness on palpitation as well as the signs of "cardiac memory" in the ECG resisted both, so that we were forced to rule out further arrhythmias as trigger mechanisms for the identified

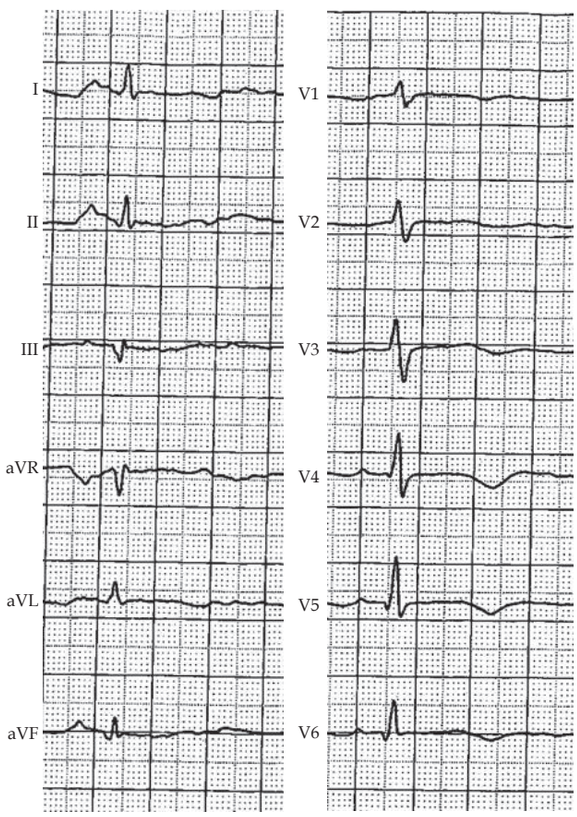


**Figure 1** ECG of the Patient during admission. Shown here is the regular sinus rhythm at the rate of 62/min., terminal negative T-waves in V1-6 and Q-waves in III, aVF as demonstrated in respective ECG's.

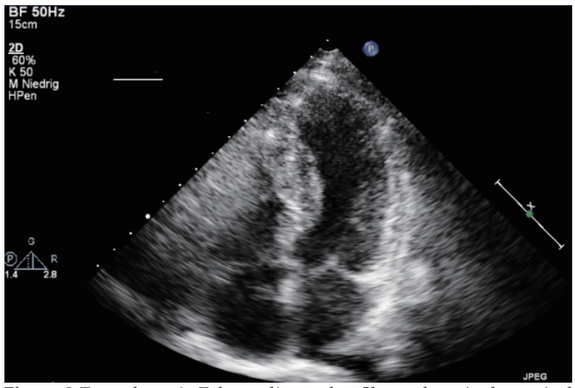


**Figure 2** Transthoracic Echocardiography. Shown here is the typical apical four-chamber view frozen in systole with reduced left ventricular function, ejection fraction measured to 40% (Simpson) and apical akinesia.

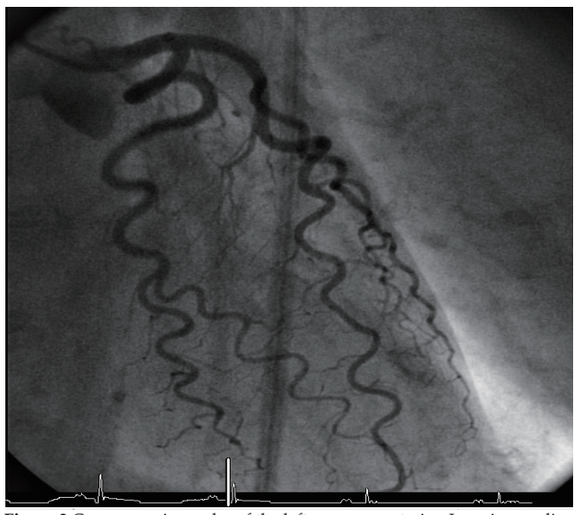

**Figure 3** Coronarangiography of the left coronary arteries. Invasive cardiac catheterization was performed. The contrast enhanced angiography (10ml Imeron 350, applied manually) of the left coronary artery systems reveals inconspicuous, clean and smoothly perfused arteries. The right coronary artery looked the same (data not shown). The coronary artery disease could be rule out completely. Here frozen in diastole.

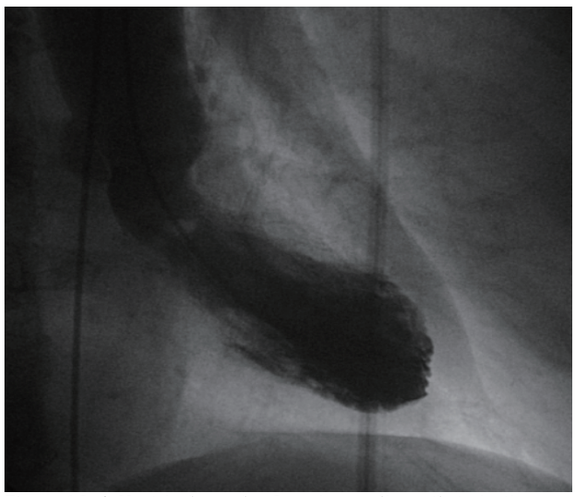

**Figure 4** Left Ventriculography. Invasive cardiac catheterization was performed as mentioned above (see figure 3). The contrast enhanced left ventriculography (pressure guided application: 10ml/sec; volume of Imeron 350: 25ml) revealed the typical apical ballooning for Tako-Tsubo Cardiomyopathy. Here frozen in systole.

Tako-Tsubo Cardiomyopathy. We performed an electrophysiological examination with normal, inconspicuous findings.

Further examinations (holter ECG to rule out unidentified arrhythmias, the sonography of the complete abdomen; the gastroscopy and the coloscopy) were completely without any pathological findings.

We suggested Adalimumab as trigger for the Tako-Tsubo Cardiomyopathy and stopped immediately the treatment. Therefore, we increased Methotrexat to 20 mg per week resolving the symptoms and improved left ventricular function to the normal status without any further regional wall motion irregularities. Finally, the patient was under healthy and stable condition at discharge.

## DISCUSSION

Tako-Tsubo Cardiomyopathy is a cardiac distress syndrome triggered through sympathetic nervous stress like anger, anxiety, pain, dyspnoea[1] or others[2]. Clinically, patients with Tako-Tsubo Cardiomyopathy suffer acute chest pain, dyspnoea, or cardiac syncope leading to specific disease related alterations in ECG (ST elevations or terminal negative T-waves), in transthoracic echocardiography (apical hypo- to akinesia), or in invasive cardiac catheterization (left ventricular dysfunction with apical ballooning, and no signs of coronary artery disease). Cardiac myocardial markers as Creatininkinase or Troponin I show increased levels typical for the pathological mechanism behind the Cardiomyopathy: reversible myocardial sympathetic nervous stress with additional catecholamine overload of the left ventricular[5,6].

Due to the reversible manner of the disease, (1) all findings resolve without further specific treatment[2] and (2) there are only betablockers established to reduce the recurring occurrence of the disease[3]. A general treatment suggestion is the reduction of psychic stress for the patient[1]. Further, (3) in cardiac shock, only intra-aortic pulsation treatment is established to secure the left ventricular function while catecholamines have to get discontinued[7].

In the literature, other mechanisms are described triggering Tako-Tsub Cardiomyopathy. i.e. patients applied with Trastuzumab or with immunglobulines[4]. Here, first and exclusively, we are demonstrating a new tumor necrosis factor-alpha antibody (TNF-alpha antibody: Adalimumab) as potential trigger for Tako-Tsubo Cardiomyopathy lacking any sympathetic nervous stress.

This is a new human monoclonal antibody[8] binding to the TNF-α antigen and is established in chronic rheumatoid arthritis[9]. Side effects are opportunistic infectious diseases. In respect, contra indications are active tuberculosis, or sarcoidosis, as well as heart failure NYHA III-IV[10,11].

The chronic inflammatory disease rheumatoid arthritis (RA) assesses primarily articulations and secondarily extra-articular systems like i.e. the cardiovascular system[12]. The grade of inflammatory activity of the rheumatoid arthritis is known as established risk factor for coronary atherosclerosis. This increased risk may be attributable to RA-specific risk factors such as hyperhomocysteinemia, disease-related dyslipidemia or vascular inflammation, or to morbidity related to medications and high levels of TNF-alpha. The possible roles of TNF-alpha in the development of atherosclerosis include the recruitment of inflammatory cells to the site of injury or the promotion of adverse vascular smooth muscle cell remodelling. TNF-alpha may also act as a proinflammatory factor in plaque rupture[13].

In contrast, Anticytokine therapy could prove beneficial in the treatment of patients with heart failure[13]. While early studies supported this hypothesis, anti-TNF strategies have not demonstrated salutary benefits in large multicenter randomized and placebo-controlled clinical trials in patients with symptomatic heart failure[13]. There is a variety of possible explanations for the failure of anti-TNF therapy: (1) TNF antagonism has untoward effects in the setting of heart failure; (2) the biological agents used in the trials were intrinsically toxic; (3) sex and race may have important implications in the outcome after anticytokine therapy; (4) the TNF-alpha protein contains a polymorphism, and, in fact, genoma plays a role in modifying the pharmacologic response to anticytokines; (5) anti-TNF-alpha approaches could have had pharmacodynamic interactions with other heart failure medications; and (6) the patients in these trials may have been inappropriately selected. These disappointing results may determine controversial attitude in the long-term treatment with anti-TNF agents in RA[14].

The effects of TNF-alpha blockers on incident cases of congestive heart failure (CHF) in RA are controversial. Here, in this case, the disease was steady-state in remission under immune suppressed therapy [chemically in the blood test no signs of active inflammation]. In the transthoracic echo we ruled out pericardial or myocardial involvement while left ventricular function got resolved to a normal staus by discontinuation of TNF-alpha antibody treatment. Direct TNF-alpha effects on the left ventricular function are to disclose[13]. Further, the ventricular function was primarily normal and got completely resolved (improved) after the acute/ active phase of the disease (Tako-Tsubo Cardiomyopathy). In general, the following suggestions were established through the guidelines for the treatment of RA: (1) RA patients with history of CHF and a concomitant indication for the use of TNF-alpha blockers do not need a baseline cardiac evaluation to screen for heart failure; (2) patients with well-compensated mild CHF New York Heart Association (NYHA) classes I and II and a concomitant indication for the use of TNF-alpha blockers should be evaluated at baseline and then be closely monitored for any clinical signs of worsening heart failure; and (3) patients with (NYHA) class III or IV heart failure should not be treated with TNF-alpha blockers in any case[14].

## CONCLUSION

Adalimumab, a new TNF-α antibody, applied in chronic rheumatoid arthritis may directly trigger Tako-Tsubo Cardiomyopathy without any sympathetic nervous stress. Hence, monitoring of either clinical symptoms (palpitations) or the left ventricular function [through transthoracic echocardiography] is indicated while Adalimumab is applied. When Tako-Tsubo Cardiomyopathy occurs, the immediately discontinuation of the treatment with Adalimumab resolves left ventricular function and clinical symptoms.

However, it would be ambitious to conclude from a single case observation that Adalimumab causes Tako-Tsubo Cardiomyopathy. The authors hereby recommend a clinical trial to test this hypothesis in a multi-center fashion.

Sympathetic nervous stress is widely known as trigger for Tako-Tsubo Cardiomyopathy. However, the increasing number of other findings (like i.e. Adalimumab) as pathological mechanism triggering Tako-Tsubo Cardiomyopathy suggests the need for further studies of this specific disease.

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## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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CASE REPORT

# Severe Pulmonary Embolism with Negative D-Dimer-Testing

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## ABSTRACT

A 46 year old female Caucasian was admitted with shortness of breath on exertion, productive cough and hemoptysis few days of duration without any other chronicle diseases. She had recent history of sigmadiverticulitis treated with antibiotic and hysterectomy a year ago because of hypermenorrhoe. Vital signs were stable without any clinical signs of a deep venous thrombosis. The electrocardiogram (ECG) showed sinus rhythm with an incomplete right bundle branch block. Laboratory tests revealed a negative d-dimer (Latex-method). We assessed a contrast enhanced computed tomography scan (CT) of the chest illustrating surprisingly a severe pulmonary embolism in the right lung (main bronchus of the lower lob). Several further examinations ruled out malignant diseases or favorable thrombosis. Treatment of the patient was established using low molecular weight heparin (subcutaneously administered), switched to rivaroxaban at the end of the in-hospital duration. Discharge was carried out after eight days in stable conditions. Anticoagulation was prescribed for three months. D-dimer testing is clinically established to rule out embolism/thrombosis laboratorial despite of arterial or venous location. This is a unique case, where the laboratorial testing failed to detect a severe pulmonary embolism while the sensitivity for the d-dimer testing tends in general high. Clinically, the imaging approach (computed tomography scan of the chest) reflects "the gold standard" for pulmonary embolism in contrast to the d-dimer testing.



**Key words:** Severe pulmonary embolism; Negative d-dimer testing; Hemoptsis

Dagkiran H, Atas R, Tomic I, Plachtzik C, Geisler T, Gawaz MP, Oberhoff M, Anger T. Severe Pulmonary Embolism with Negative D-Dimer-Testing. *Journal of Cardiology and Therapy* 2015; 2(1): 265-268 Available from: URL: http://www.ghrnet.org/index.php/jct/article/view/1033

## INTRODUCTION

Due to the high sensitivity of the d-dimer-test[1] - in general, the d-dimer test is used to demonstrate the specific diagnosis of pulmonary embolism or deep vein thrombosis[2]. In contrast, a negative d-dimer-testing rules out severe pulmonary embolism in high probability[1,2]. Here in this specific case report, we are demonstrating a 46 year old female Caucasian suffering acute severe pulmonary embolism identified through thoracic CT without elevated d-dimer levels in the laboratory. This case is important and needs to be reported due to the lack of elevated d-dimer testing even when severe pulmonary embolism occurred.

## CASE REPORT

A 46 year old female Caucasian was admitted with shortness of breath on exertion, productive cough and hemoptysis since few days without any other chronical diseases. She had recent history of sigma diverticulitis treated with antibiotic and hysterectomy a year ago because of hypermenorrhoe. Patient was still active on nicotine (2 pack years). Orally informed consent was obtained from the patient for publication of this case report and any accompanying images.

Clinically we found a woman in a good general condition and normal nutritional status, awake, oriented, her blood pressure 100/70

mmHg, her pulse 62/min, her respiratory rate increased 21/min, oxygen saturation of 97%, no pathologic murmurs, auscultation of the lungs reveals no bilateral wheezes and rales, unobtrusive physical examination.

Laboratory tests resulted negative for d-dimer-testing three times with the Latex-method (0.28/0.33/0.45), other laboratory values were within normal range. The ECG showed a sinus rhythm at the rate of 62/min., incomplete right bundle branch block, without excitation abnormalities (Figure 1). X-ray of chest revealed the contour of a diaphragm in regular and deep standing manner, compatible with a pulmonary emphysema, no pneumonia, mediastinum wasn't widened, no stasis and enlargement of the heart, aorta was according to age. The transthoracic echocardiography was completely with normal findings. For further acute analysis, we performed a contrast enhanced CT-scan of the chest and figured out an embolism of the pulmonary artery of the lower lobe without infarction, without round lesions or enlargement of the lymph nodes (Figure 2).

Further examinations (the sonography of deep veins and of complete abdomen; gynecological examination; the CT-scan of the abdomen; the gastroscopy and the coloscopy) were completely without any pathological findings except for diverticulosis without signs of acute activation, two hemangiomas in the liver, a liver cyst in the left liver lobe.

The appropriate treatment for this patient without cardiovascular instability was anticoagulation with low molecular weight heparin, which was subcutaneously administered during the several examinations. During the in-hospital duration we switched the anticoagulation therapy to rivaroxaban per oral[3]. Hospital discharge was carried out after eight days in stable condition.

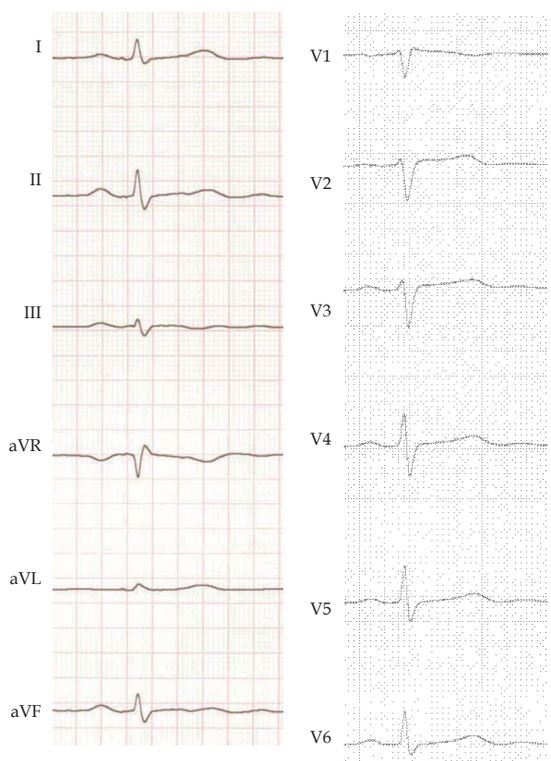


**Figure 1** ECG of the Patient during admission. Shown the regular sinus rhythm at the rate of 62/min., incomplete right bundle branch block, without excitation abnormalities as indicated in respectively ECG's.

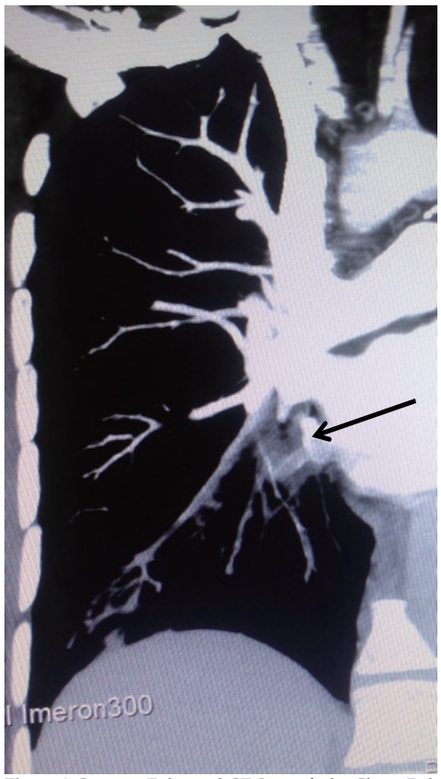


**Figure 2** Contrast Enhanced CT-Scan of the Chest. Pulmonary embolism detected in the main bronchus of the lower lob of the right lung without signs of infarction, infiltrations or tumors. The black arrow marks the thrombosis in the right lower bronchus.

## DISCUSSION

D-dimer is a fibrin degeneration product and is generated during a fibrinolysis reflecting a diagnostic method for assessing coagulation activity[4]. Several independent methods to measure the d-dimer activity (quantitative production of d-dimer) such as ELFA, ELISA, Latex- and whole blood assays (Table 1) are established[5]. D-dimer-testing is used in the diagnosis of suspected thrombotic disorder (deep venous thrombosis, pulmonary embolism, disseminated intravascular coagulation) (Table 2). A negative d-dimer-test is clinically reducing the probability of thrombotic disorder in patients without severe diseases, anticoagulation therapy, recent surgery and pregnancy[4]. In addition there are many causes of quantitative high-level of d-dimer for example: heart diseases, heart attack, pneumonia, cancer, advanced age and infectious diseases (Table 2)[6].

A pulmonary embolism is caused through an embolus in the pulmonary artery due to (i) high degree of coagulation[7], high degree of cardiac thrombosis[7] or high degree of endothelial disorders of the pulmonary arteries[7,8]. A blood gas analysis in patients with pulmonary embolism shows hypoxemia and hypokapnia[9]. The ECG shows signs of right sided ventricular strain, SIQIII-type, complete right bundle branch block[10]. A contrast enhanced *CT-scan* of the chest is a special diagnostic method to find pulmonary embolisms with a sensitivity of 86-100%[11]. This disease is the most common unrecognized cause of death[9]. Approximately 95% of pulmonary embolisms derive from thrombosis in the vena cava inferior[1]. Typical clinical signs are: dyspnea/ tachypnea, tachycardia, cyanosis, chest pain, cough, hemoptysis, dizziness, sweating, syncope (in the short term)[12] The clinical condition ranges from asymptomatic to

threatening condition in cardiac shock[12]. There are several risks of pulmonary arterial embolisms: immobility, previous trauma, operations, smoking, varicose veins, congestive heart failure, female gender, pregnancy, contraceptives, obesity, advanced age, drying out and rare vascular anomalies[12]. If there is a presence of recurrent thrombosis pathological findings such as antiphospholipid syndrome, protein C and S deficiency ATIII-deficiency, polyglobulia, polycythemia vera and malignant diseases should be ruled out[6].

Due to the high sensitivity of the d-dimer-test[1] - in general, the d-dimer test is used to demonstrate the specific diagnosis of pulmonary embolism or deep vein thrombosis[2]. Thereby, a negative d-dimer-testing rules out severe pulmonary embolism in high probability[1,2].

## CONCLUSION

Because of the high incidence of early lethality in patients with acute pulmonary embolism reflecting clinically symptoms such as dyspnea/tachypnea, tachycardia, cyanosis, chest pain, cough, hemoptysis, a fast resolving therapy is very important. Therefore, clinically we demand an individual diagnostic concept. D-dimer-test is broadly used to determine pulmonary embolism or deep vein thrombosis. A negative d-dimer-testing rules out a severe pulmonary embolism with high probability[2]. Additionally, the sensitivity of the d-dimer-test depends on the used diagnostic method (Table 1) or further malignant and infectious diseases (Table 2).

**Table 1** Systems for d-dimer testing.

| Method | Type | Manufacturer |
|---|---|---|
| Immunofluorescence immunoassay | ELFA | VIDAS® |
| Immunoadsorption assay<br>microplate immunoassay<br>membran-immunoassay | ELISA | Asserachrom®<br>NycoCard®<br>Cardiac Reader®<br>Instant IA® |
| Latex-method | | Tinaquant®<br>STA-lia-test®<br>HemosIL |
| Whole blood assay | | SimpliRed®<br>Simplify® |

**Table 2** Causes of elevated d-dimer levels.

| | |
|---|---|
| **Permanently increased values in blood** | aortic aneurysm<br>other vascular aneurysm<br>hemangiomas<br>Kasabach-Merritt-Syndrome<br>other vascular malformation<br>several shunts<br>malignancies in particular adenocarcinoma<br>several hematological cancer |
| **Acute increased values in blood** | venous or arterial thrombosis<br>pulmonary embolism<br>peripheral or coronary arterial embolism<br>trauma<br>recent surgery<br>burns<br>hematoma<br>aortic dissection<br>sepsis<br>severe infections<br>erysipelas<br>HELLP-syndrome<br>hemolysis<br>HIT type2 (heparin-induced thrombocytopenia) |

Hence, we suggest primarily an imaging diagnostic method (CT scan of the chest) to determine pulmonary embolism in regard to the irregularities in the quantitative determination of d-dimer levels. A d-dimer-test alone is not sufficient.

## ACKNOWLEDGMENTS

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## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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CASE REPORT

# Cardiac Computed Tomography for Detecting Intracoronary Thrombotic Structures in Proximal LAD Bare Metal Stents

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## ABSTRACT

Thrombus distribution is known part of atrial arrhythmias. We here report a clinical example using cardiac 256-multidetector row computed tomography (256 MDCT) for examination to assess for small intracoronary thrombotic structures in proximal parts of vessels with either big size (> 2,5 mm diameter) and/ or existing bare metal stents on a 70 years old male individual. He was suffering a non ST elevated myocardial infarction due to intracoronary thrombus in bare metal stents in the proximal left artery descending (LAD) in regard to occult atrial fibrillation. Philips 256 iCT documented the small amount of rest thrombus after abciximab pre treatment before discharge of the patient under acetylsalicylacid (100mg) and phenprocoumon (for 6 months). Summarised, this example proposes and underlines further use of cardiac MDCT for patients with acute chest pain to improve prognostic outcome by reduction of complications. Additionally, even 3 years after bare metal stent implantation in big vessels, here proximal LAD, we are mainly demonstrating the need of continuous antithrombotic acetylsalicylacid treatment to avoid in-stent thrombosis.



**Key words:** Cardiac 256-MDCT; Intraluminal Bare Metal Stent Thrombus; Acetylsalicylacid; Abciximab

Anger T, Bernhard B, Claudia P, Martin O, Martin H. Cardiac Computed Tomography for Detecting Intracoronary Thrombotic Structures in Proximal LAD Bare Metal Stents. *Journal of Cardiology and Therapy* 2015; 2(1): 269-272 Available from: URL: http://www.ghrnet.org/index.php/jct/article/view/1034

## LEARNING OBJECTIVE

Further use of Cardiac CT is the detection of intraluminal thrombotic material in coronary stents.

## CASE REPORT

A 70 years old male patient in good health conditions with known coronary artery disease
and existing three bare-metal stents (Cobalt-Chronium "Multi-Link Vision Bare-Metal Coronary Stent System, 3.0×12mm, Abbott, Wiesbaden, Germany) in the proximal and mid part of the left anterior descendents artery (LAD) implanted 3 years ago, was presented to the Department for Cardiology with acute chest pain for 2 hours following chemically a Non-ST-Elevated Myocardial Infarction (NSTEMI).

In the past, a common drug treatment was established with 100 mg acetylsalicylacid per day, 2.5 mg bisoprolol per day, 10 mg ramipril per day, 20 mg simvastatin per day and for 4 weeks clopidogrel 7 5mg per day after bare-metal stent-implantation. The 100 mg acetylsalicylacid treatment was discontinued due to an elective surgery on the right carotid artery interna 2 weeks before hospital presentation in regard to severely stenosis.

Actually, the Troponin I level raised to 1.5 ng/mL (normal < 0.05ng/

mL) and the ECG demonstrated an paroxysmal atrial fibrillation turning in normal ventricular frequency (to this date unknown). Immediately, an invasive coronary angiography was performed and the coronary status was assessed revealing a remarkable structure in the proximal two stents of the LAD suspected to an intracoronary thrombus while normal perfusion was determined in all stents and the rest of the vessel (TIMI 3), see figure 1 (pre, marked through white arrows).

Due to an intraluminal reduction of only 30% Diameter Stenosis in both proximal LAD stents, abciximab adjusted to the body weight was given intravenously for 12h and a second look was assessed using Philips iCT Cardiac 256-MDCT while the patient spontaneously converted into normal sinus rhythm (Figure 2). Retrospective gating to 75% RR interval was performed (heart rate 65 beats per minute) and only a small rest thrombus in the proximal LAD stent surrounded by non- and calcified plaques as well as the struts of the both "Vision" stent systems (only 0.0032" thick) were observed (see bold white arrow, figure 2). The complete vessel demonstrated further almost inconspicuous perfusion. Caused through additional unspecific symptoms of the patient, we performed a second invasive coronary angiography with complete normal perfusion in all LAD stents (proximal and mid) and ruled out further intravascular thrombotic materials, see figure 1 (post).

The patient got discharged 2 days later set on Phenprocuomon for 6 months due to stable sinus rhythm improved by beta-receptor inhibition (metoprolol 95 mg per day) added to 100 mg acetylsalicylacid per day.

## DISCUSSION

While thrombus distribution is known part of atrial arrhythmias[1-4], this example reveals cardiac 256-multidetector row computed tomography (256 MDCT) as clinical examination to explore small intracoronary thrombotic structures in proximal parts of vessels with either big size (> 2,5 mm diameter) and/or existing bare metal stents[5].

The thrombotic structure in the LAD stents is caused through the discontinuing of 100 mg per day acetylsalicylacid treatment. The obviously distribution of the thrombotic material in the vessel is focusing mainly in the stent regions which excludes coronary embolisms through atrial arrhythmias as reason for the intraluminal thrombus.

We support a further use of cardiac CT detecting intraluminal thrombotic material following (1) coronary calcium scoring[6], (2) coronary plaque formations[7-9], (3) coronary artery disease[10,11], (4) left ventricular function (mass, regional wall motions, ejection fraction)[12,13], (5) right ventricular function[14], (6) valve function (aortic valve)[15], and (7) the detection of the culprit lesion in myocardial infarction[16-18].

Infusion of abciximab as antithrombotic treatment regimen is part of the drug management in acute coronary symptoms[19-22]. Here, partial success for thrombus lysis was assessed detected through cardiac 256-MDCT while even complete thrombus abolishment was assumed using conventional invasive coronary angiography (see figure 1, lower panel.).

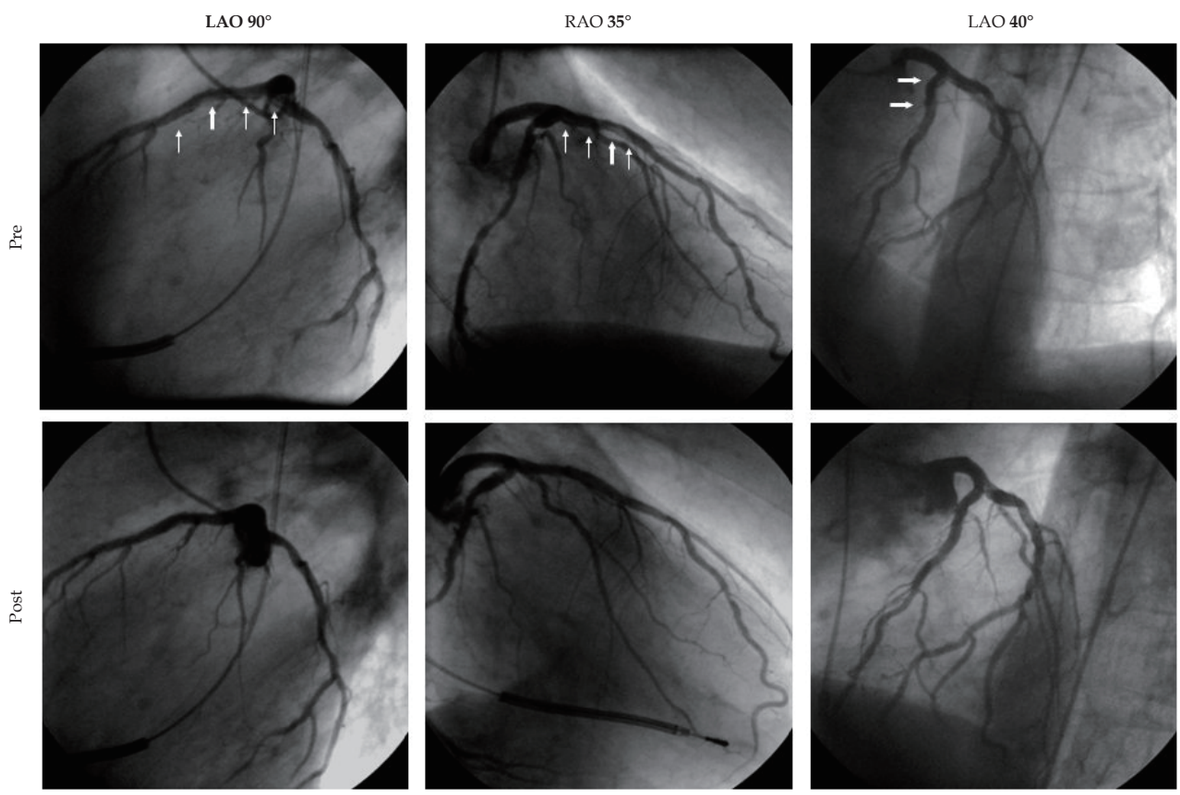


**Figure 1** Invasive Coronary Angiography. Demonstrated here are slides from the invasive coronary angiography determining the intracoronary thrombotic structure in the two bare metal stents (Multi Link Vision Coronary Stent System, 3.0x12mm, Abbott, Wiesbaden, German) in the proximal left anterior descendents artery (LAD) as marked with white arrows. The upper panel (pre) shows the coronary status of the LAD in different ankles (LAO90°, RAO35° and LAO40°) as well as of the circumflex artery right after administration of the patient in the Department for Cardiology 2 hours after begin of symptoms (acute chest pain). The lower panel is demonstrating the coronary status after intravenous support of abciximab for 12 hours (post) in same angiographic ankles.

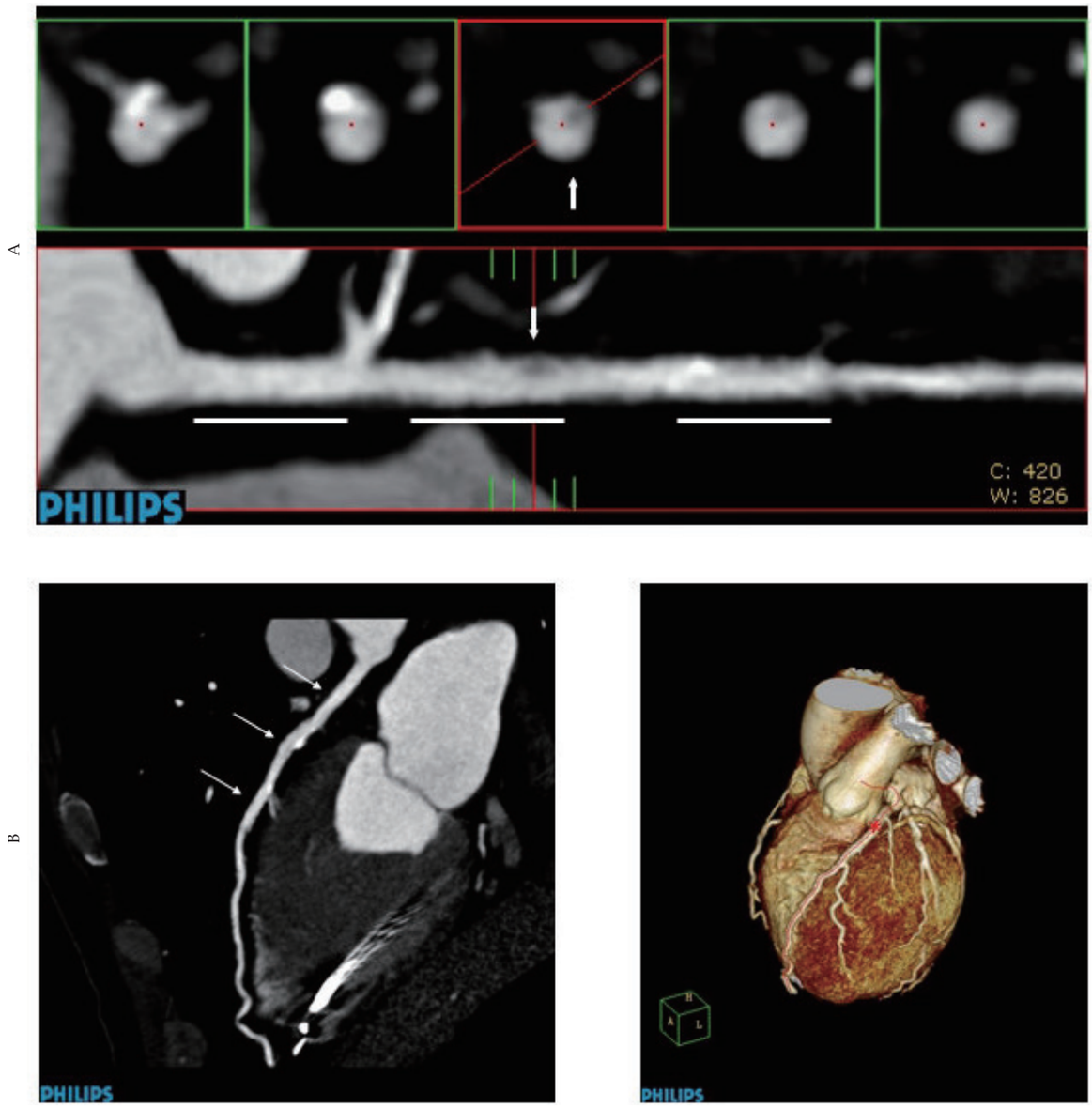


**Figure 2** Cardiac 64-MDCT. Retrospektives Gating in 75% RR interval, heart rate 65/min in sinus rhythm revealed 12 hours after abciximab treatment demonstrated slides exploring small dark structure suspected for rest thrombotic material as marked with white arrow in the proximal LAD stent (marked with white lines). A. Demonstrated here are computer based reconstruction of strengthen LAD vessel (lower panel, axial cut) with the three stents (white lines) and the suspected thrombotic material (dark structure, marked with white arrow). In the upper panel, cross axial cuts are demonstrating only the 30% Diameter Stenosis caused through the thrombus in the LAD stent. B. Coronary curved section cuts demonstrating reconstructed contrast perfusion in the LAD. Highlighted here are the three stent positions (left panel, white arrows) and the 3D reconstruction with the red coloured marked LAD (right panel).

This example proposes and underlines further use of cardiac MDCT for patients with acute chest pain to improve prognostic outcome by reduction of complications[23]. Additionally, even 3 years after bare metal stent implantation in big vessels, here proximal LAD, we are mainly demonstrating the need of continuous antithrombotic acetylsalicylacid treatment to avoid in-stent thrombosis.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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